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CALCIUM AND PHOSPHORUS METABOLISM IN NEPHRITIS

BY

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Modern methods of biochemical research have revealed certain changes to be more or less constantly present in the blood of persons suffering from renal disease. Many of these variations are still imperfectly understood. Some of the earlier hypotheses as to their causation have had to be abandoned, and others have not as yet been definitely confirmed or disproved. The question of 'retention of phosphorus' falls into the latter group and it was primarily with a view to elucidating this question that the present work was undertaken. Since, however, retention of phosphorus is intimately associated with that of calcium, the metabolism of calcium was investigated at the same time.

In 1916 Marriott and Howland[1] showed that in nephritis with low urinary excretion, the inorganic phosphorus content of the serum was high. These results have been confirmed by other workers and the theory of phosphorus retention has been generally accepted. Likewise, the observations of Halverson, Mohler and Bergeim[2] in 1917, of low serum calcium and decreased urinary calcium have been frequently corroborated. These results were not questioned until 1926 when Boyd, Courtney and McLachlan[3] supplied the first available information on the utilization of these substances in renal disease, and their studies, though inconclusive, seemed to throw doubt on the occurrence of any abnormal retention of phosphorus. Consequently the accepted explanation of the low serum calcium values on the basis of compensating over-excretion became unsatisfactory.

In 1927 Byrom and Kay[4] cast still more doubt on the idea of excessive phosphorus retention by demonstrating that the total blood phosphorus showed no increase in nephritic subjects. They found merely a redistribution of the acid-soluble phosphorus, whereby the inorganic fraction increased at the expense of the non-hydrolyzable ester phosphorus of the red corpuscles, thereby supporting the conclusions of Boyd, Courtney and McLachlan.

In view of the conflicting evidence as to their utilization in renal disease it seemed worth while to investigate by balance studies the metabolism of calcium and phosphorus. While this was being done, observations were made on the serum values. The results, in agreement with those of other workers, showed subnormal values for calcium and high figures for inorganic phosphorus during the more acute stages of the disease.

The main part of the work is presented in three sections :—

I. Utilization of calcium and phosphorus in nephritis, i.e., calcium and phosphorus balances.
II. Absorption of calcium and phosphorus in nephritis.
III. Excretion of calcium and phosphorus in nephritis.

* Substance of thesis submitted for Degree of M.D., Glasgow University.

I. UTILIZATION OF CALCIUM AND PHOSPHORUS IN NEPHRITIS.

As has already been indicated, the only previous calcium and phosphorus balance studies in nephritis are those of Boyd, Courtney and McLachlan[3]. They found that nephritic children had a positive calcium balance unless the intake was very low, and that the amount of calcium retained could not be correlated with the blood calcium content. All the œdematous subjects showed a positive phosphorus balance except two who were on minimal intake, and the non-hydræmic patients in most instances had negative balances. They concluded that 'evidence of phosphate retention given by blood and balance studies does not always agree.'

These observations must be looked upon with caution as the duration of the balance period was in each case only two or three days. The fallacies of such short periods have been frequently demonstrated. Apart from this, however, they do not quote control observations of their own, but used the normal figures of Sherman and Hawley[5] for comparison with figures for nephritic patients.

In the present work the calcium and phosphorus balances were determined in a number of nephritic children in each of whom clinical and biochemical data gave evidence of renal damage. The procedure followed was similar to that observed in other balance studies in this hospital. Diet was confined entirely to milk, approximately 100 c.cm. per kilogramme of body weight being allowed daily. Where the quantity, so calculated, was thought to be excessive, sugar was substituted for some of the milk, and by this means the caloric value of the diet was maintained. Each child was given the selected diet for at least three days before the collection of excreta was commenced.

Balance studies must ever be open to criticism until some method of marking the fæces is introduced, whereby collection of the appropriate specimens may be made with certainty. Bergeim's suggestion, that a carmine capsule be given with the first and last meals of the period, was tested in several normal children. The dye was found to be spread throughout the intestinal evacuations of 48 hours and the method accordingly was abandoned. In subjects where there was a tendency to constipation lavage was used daily. In all cases the bowel was washed out with sterile water at the beginning and at the end of each period.

Balance studies were carried out on eleven nephritic children, representing various phases of renal disease. Nine were classed as 'acute nephritis' since clinical recovery seemed complete within six months. The two remaining subjects suffered respectively from chronic interstitial nephritis accompanied by dwarfism (Case 6) and chronic parenchymatous nephritis (Case 4). In four of the acute cases a second balance period was observed after an interval varying from one to four months.

Control figures were obtained from three children who had recovered from acute ileo-colitis, bronchitis and rheumatism respectively. The details of the analyses are given in Table 1.

It has been shown by Telfer[26] that the retentions of CaO and P_2O_5 in healthy children are approximately equal and vary from 0·06 to 0·12 grm.

per kgrm. per day. Sherman and Hawley[5] observed that in children between 3 and 12 years of age, on a mixed diet with 750 c.cm. of milk daily, the average retention of CaO was 0·01 grm. and of P_2O_5 0·008 grm. per kgrm. per day. They found that when the milk allowance was increased, the retentions of CaO and P_2O_5 rose. Therefore, since each child of the present series was having considerably more than 750 c.cm. of milk daily, the retentions might reasonably be expected to show values over 0·01 grm. per kgrm. per day.

MacRae[6], working in this laboratory, found that in convalescent children between 3 and 12 years of age, on a diet consisting entirely of milk, the reten-

TABLE 1.

CALCIUM AND PHOSPHORUS INTAKE AND EXCRETION IN NEPHRITIC SUBJECTS (CASES 1–11) AND NORMAL CONTROLS (CASES 15–17).

Case No.	Age in years	Weight kgrm.	Days of study	CaO in grm. per day			Balance grm. per kgrm. per day	P_2O_5 in grm. per day			Balance grm. per kgrm. per day
				Intake	Urine	Fæces		Intake	Urine	Fæces	
1	8	26	6	4·65	·044	2·61	+·077	6·54	2·45	1·575	+·096
2	6	16·4	6	3·234	·039	2·277	+·057	4·536	1·69	1·75	+·068
3	12¼	26	7	4·8	·087	3·29	+·054	6·6	1·84	3·24	+·058
	12 7/12	27·4	6	3·84	·136	2·41	+·048	5·67	1·92	2·31	+·053
4	13	25	4	2·7	·021	1·58	+·044	3·78	·32	2·11	+·054
5	8	26·4	6	2·293	·063	1·14	+·042	3·216	1·02	1·212	+·038
	8 1/12	24·4	6	2·212	·038	1·62	+·023	2·884	·938	1·597	+·014
6	6	11·6	7	2·232	·088	1·74	+·035	3·08	·82	1·827	+·039
7	10	22·6	5	3·06	·041	2·46	+·025	4·36	1·87	2·038	+·02
8	6	18·8	5	2·1	·048	1·58	+·025	2·52	·764	1·44	+·017
	6 5/12	17·5	6	2·15	·073	2·308	—·013	3·18	1·197	1·977	+·0003
9	5	15	6	1·95	·022	1·8778	+·0033	2·73	·914	1·803	+·00083
	5 3/12	14·8	6	2·13	·0575	2·0965	—·0017	2·86	1·217	1·98	—·225
10	6	13·8	5	1·575	·046	1·53	—·0007	2·1	·81	1·49	—·014
11	8	20	7	2·79	·03	3·101	—·017	3·96	1·1	3·18	—·016
15	7	21·3	6	3·1	·2362	1·115	+·081	4·4	2·147	·717	+·071
16	6	20	6	2·87	·135	1·89	+·042	3·83	1·26	1·82	+·037
17	6	15	6	2·325	·166	1·603	+·037	3·3	1·408	1·205	+·046

tions of CaO and P_2O_5 were approximately equal and ranged between 0·016 and 0·052 grm. per kgrm. per day. The three control subjects of this series showed a similar state of affairs, the retentions varying between 0·037 and 0·081. (To avoid repetition hereafter all utilization figures will be merely stated in grammes on the understanding that they have been calculated in terms of body weight for one day.)

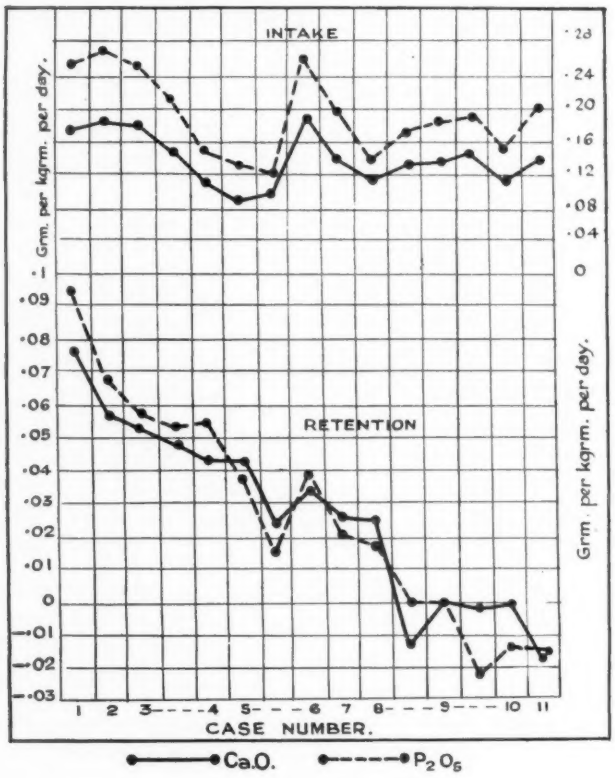
It is important to emphasize that Telfer found in young children retentions of calcium as high as 0·12 grm. and Holt, Courtney and Fales[7], working with healthy infants, retentions averaging 0·09 grm. These being the highest figures recorded for healthy children, it might be expected that in the presence

of any ' retention ' in nephritic subjects the balances would be at least as great. The utilization figures (Table 1) show that this expectation was not realized. The highest figure of the series was 0·096 grm., the remainder being less than 0.08 grm.

In these fifteen determinations the balances varied to a marked extent. In eleven the CaO balance was positive, in four negative ; while the P_2O_5 balance was negative on three occasions. Holt, Courtney and Fales[7] state that an intake of less than 0·09 grm. of CaO per kgrm. per day will produce either a very low retention or a negative balance. The intake in this series

CHART I.

Ca. AND P. INTAKE CONTRASTED WITH Ca. AND P. RETENTION.



was only in one instance as low as 0·09 grm. and averaged 0·14 grm. CaO and 0·183 grm. P_2O_5. It would therefore appear that the supply of both was adequate. From Chart I it will be seen that utilization bears no relationship to intake. The cases showing negative balances received a more ample supply than some of those with a positive retention. Similarly high retentions are shown to be quite unconnected with the intake.

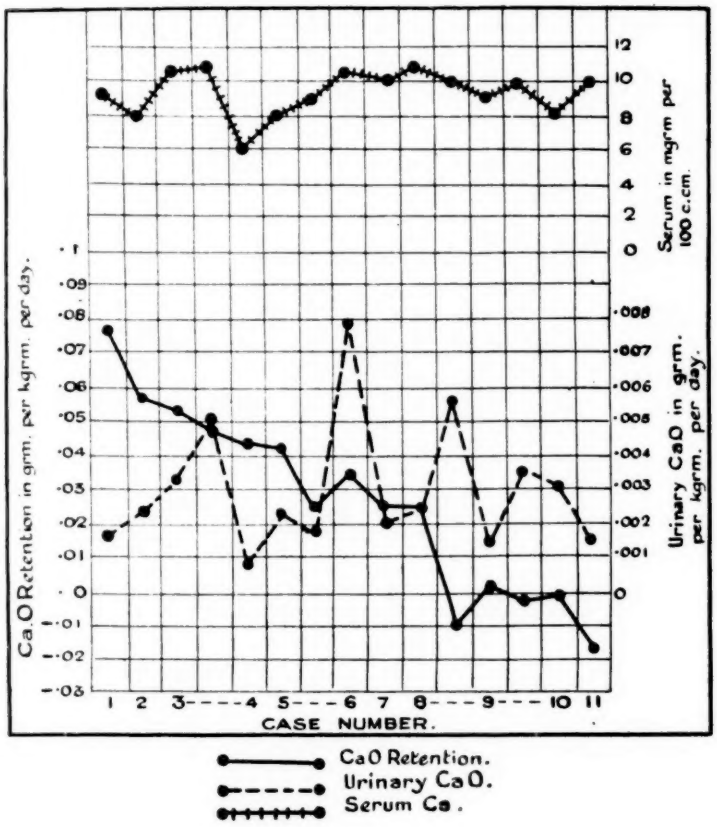
Neither the age nor the weight of the children could be correlated with the utilization of either CaO or P_2O_5.

In the four cases in which balance periods were observed on two occasions, the retentions during the second period were diminished (Table 1). In one of

these (Case 3) the difference in the balance figures might well be attributed to the slight decrease in intake. In each of the other three cases, however, this explanation is inadmissible, for two reasons: (1) the intake during each period was practically identical; (2) the decreased retention was very definite and of such magnitude that in two children a negative balance was found. These latter figures were obtained while the children were definitely convalescent, and it may be significant that the only other negative balances were found in two other convalescent children.

CHART II.

SERUM Ca CONTRASTED WITH CaO RETENTION AND URINARY CaO.

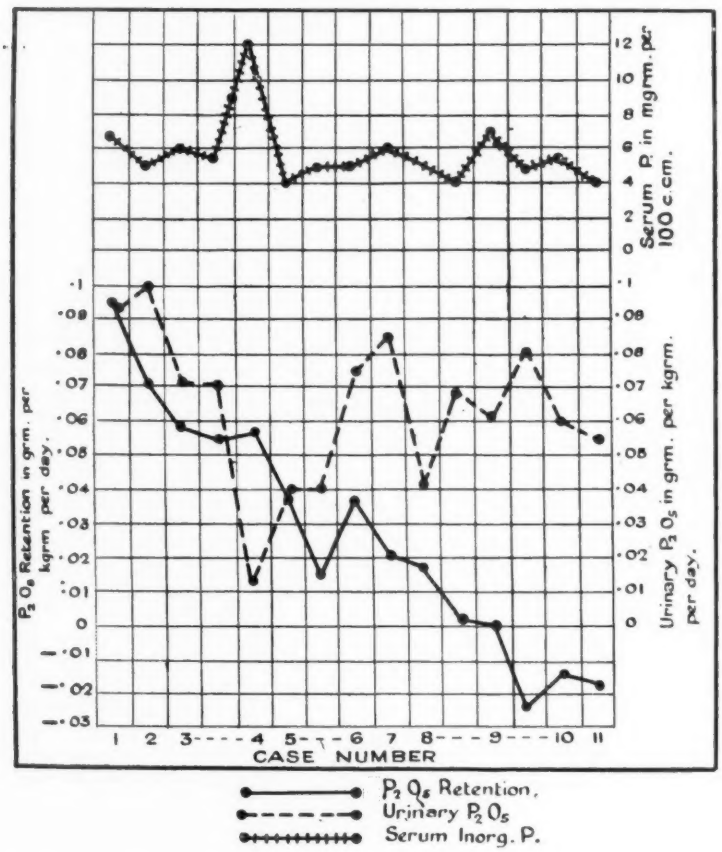

CaO Retention in grm. per kgrm. per day.
Serum in mgrm per 100 c.cm.
Urinary CaO in grm. per kgrm. per day.
CASE NUMBER.
1 2 3 4 5 6 7 8 9 10 11
CaO Retention.
Urinary CaO.
Serum Ca.

Attempts to correlate the retention figures for CaO and P_2O_5 with the urinary analysis and approximately contemporary blood observations were of no avail (Charts II and III). The levels of the serum calcium and phosphorus had no bearing on their retentions. These observations agree with those of Boyd, Courtney and McLachlan[3] that 'the calcium balance is independent of the blood-calcium content,' and 'evidence of phosphate retention given by blood and balance studies does not always agree.' Case 4 illustrates this clearly. Similarly, the levels of blood non-protein nitrogen and chloride could not be associated with the CaO and P_2O_5 balances.

The remaining point shown by these balance studies in nephritic children is the remarkable manner in which the utilizations of CaO and P_2O_5 run parallel (Chart I). This has been demonstrated in healthy subjects and in other diseases, such as rickets and cœliac disease, and apparently there is no exception in nephritis. The graphs in this chart bring out the point clearly and taking this fact into consideration it is obvious that if excessive retention of phosphorus occurs in nephritis, an approximately equal extra retention of calcium accompanies it.

CHART III.

SERUM INORGANIC P. CONTRASTED WITH P_2O_5 RETENTION AND URINARY P_2O_5.


Serum P in mgrm. per 100 c.cm.
P2O5 Retention in grm. per kgrm. per day.
Urinary P2O5 in grm. per kgrm. per day.
CASE NUMBER
P2O5 Retention.
Urinary P2O5
Serum Inorg. P.

Conclusions.—From the results so far noted it is permissible to draw the following conclusions regarding the nature of mineral metabolism in nephritis:

1. The retentions of CaO and P_2O_5 are as a rule approximately equal and within the normal range, except during convalescence when they are reduced.

2. There is no relationship between the serum levels of calcium and inorganic phosphorus on the one hand, and the retentions of CaO and P_2O_5 on the other.

3. There is no connection between the retention and the urinary excretion of either CaO or P_2O_5.

II. ABSORPTION OF CALCIUM AND PHOSPHORUS IN NEPHRITIS.

(1) **Calcium.**—The balance investigations of this study showed low urinary excretion of calcium. This has been observed on many previous occasions and the decrease has been attributed to impairment of renal function without, as in the case of phosphorus, any accumulation in the blood. Boyd, Courtney and McLachlan[3] concluded from their studies that the nephritic kidney was incapable of excreting calcium in normal fashion, citing as evidence of this the lowered urinary output and the abnormally small amount of calcium per 100 c.cm. of urine.

Before diminished excretion can be made responsible for the low urinary calcium, it must be shown that absorption is at least comparatively normal, but so far as can be ascertained from the literature this aspect of calcium metabolism in nephritis has received scant attention. Wills, Sanderson and Paterson[8] state that even in presence of a negative balance, where there is increase in urinary calcium, it is fair to conclude that there is increased absorption. Since in this study the children in whom two balance periods were observed showed an increased urinary excretion of calcium in the second (convalescent) period it seemed important to study the efficiency of absorption both during the active and the convalescent stages of the disease.

In previous studies of the effect of ingested salts on the blood calcium two methods have been employed. The earlier results, obtained after prolonged administration of calcium salts, were extremely inconclusive and contradictory, but more recent observations, in which a series of estimations was carried out at intervals after a single dose, have shown much less variance.

The striking feature of the earlier reports on absorption of calcium is the stress laid on the difference in availability of different salts. Steenbock, Hart, Sell and Jones[9] in 1923 decided that no difference in availability existed between the lactate, carbohydrate, phosphate, silicate or sulphate, so long as a sufficient quantity was supplied. Jansen[10] in 1924 found that calcium lactate, given orally, had no effect on blood calcium but found increase with the chloride and bicarbonate, particularly well marked with the latter. Hjort[11] in 1925 was of opinion that the more soluble salts, the lactate, chloride and glycerophosphate, had a much more constant effect than the less soluble carbonate.

Attempts have been made to probe this suggestion that the availability of the calcium depends on the solubility of the salt exhibited. Wills, Sanderson and Paterson[8] concluded that the gastric acidity did not seem to be a limiting factor in the supply of calcium to the body. This opinion was based on balance experiments, no observations on blood values being reported. Mason[12] in 1921 had already noted that solution of calcium in diluted HCl did not affect the rate of absorption. He also indicated that calcium lactate produced less effect on plasma calcium than did calcium chloride, and inferred that the latter was better absorbed.

Since different observers have favoured different salts, it would appear that there can be no marked difference in their suitability. The more recent workers have shown that calcium lactate is an adequate source of supply for

absorption studies, and this salt was accordingly selected as the preparation of choice in the present work. An additional point in its favour is that no change in the pH of the blood, such as occurs with calcium chloride, follows its administration.

As has been already mentioned, it is only recently that increase in blood calcium after ingestion of calcium salts has been recognized.

The earlier workers relied mainly on prolonged administration to effect an alteration in the blood level. Bergeim[13], Blum and his co-workers[14], Leicher[15], Rockwood and Burrier[16], working with nephritic subjects, and Salvesen, Hastings and McIntosh[17] working with dogs, failed to obtain indisputable evidence of any rise in blood calcium after continued oral administration of calcium salts. They omitted, however, to allow for excretion and withdrew specimens of blood for examination at irregular intervals and often days apart.

Information obtained from serial observations at relatively short intervals after ingestion of a single dose of one or other of the calcium salts has proved much more constant and reliable. Mason[12] in 1921 found slight increase in plasma calcium with a single large dose of calcium lactate, but with calcium chloride obtained a more constant effect and higher rise. Jansen in 1923 and Hjort[11] in 1925 both demonstrated increase in blood calcium after ingestion of calcium salts, and a year later Kahn and Roe[18] and Bauer and Ropes[19] confirmed this occurrence in human subjects.

They differed considerably in their conclusions. The maximum increase reported varied between the wide limits of 14 and 81 per cent. of the fasting value, and its time of occurrence from 1 to 7 hours. It was also stated by Kahn and Roe[18] that when food was given with the calcium the rate of absorption was decreased. Hjort had previously noted that administration of from 150 to 600 c.cm. of water produced in the serum calcium a decrease of 1 mgrm. which persisted for several hours.

Accordingly, before the absorption of calcium in nephritis could be assessed, it was necessary to obtain some control curves in normal subjects.

The procedure in all cases was as follows. Each subject fasted for three hours before the withdrawal of the first specimen of blood. Four grammes of calcium lactate in approximately 100 c.cm. of water were then given, and subsequent observations were made on the serum calcium at intervals of 2, 4 and 6 hours. No food or water was allowed during this period.

The seven control curves showed great similarity (Table 2). In five the maximum elevation occurred at 2 hours. In the remaining two there was a further slight increase at 4 hours. In all, the return to fasting level had been well advanced by the end of 6 hours. None of these curves showed a final reading which was below the original level.

In nephritic subjects 28 curves were observed in 16 children (Table 2). These showed variations from the normal and from one another. In 22 curves the increase 2 to 4 hours after the dose of lactate compared favourably with that in the controls, while in four of them it exceeded the rise shown in any of the normal curves. In the remaining six curves the increase was less than that shown in four hours by even the lowest of the control series. In all the nephritic curves, however, there was some evidence of absorption.

It seems, therefore, that as in normal subjects, so in children suffering from nephritis, administration of a single dose of calcium lactate orally leads to elevation of the serum calcium. As has been already indicated, in the large majority of nephritic curves the elevation corresponded to that in the control

TABLE 2.

SERUM CALCIUM OF NEPHRITIC AND CONTROL SUBJECTS AFTER INGESTION OF CALCIUM LACTATE.

Case No.	Age Years	Nephritis	Serum Ca in grm. per 100 c.cm.				Type of graph	Stage of disease
			Fasting	2 hr.	4 hr.	6 hr.		
1	11	Acute	9·0	10·04	9·7	9·24	I	Early convalescence.
3	12	Acute	10·34	11·7	10·73	9·9	II	Improving.
	+4 mth.		10·46	10·96	9·95	10·39	III	Almost well.
4	13	Chronic	5·82	6·04	5·91	5·42	II	Very ill; some œdema
5	9	Acute	7·87	8·76	7·34	7·87	III	Uræmia; some œdema
	+10 days		8·91	9·9	9·45	9·18	I	Albuminuria only.
	+2 mth.		9·24	10·31	—	9·76	I	Albuminuria persisting.
7	10	Acute	9·91	10·7	11·3	12·17	IV	Early convalescence.
	+1 mth.		9·41	10·49	9·86	10·22	III	Albuminuria only.
8	6	Acute	9·64	10·0	9·28	8·92	II	Early convalescence.
	+1 mth.		9·77	10·77	9·41	9·23	II	Late convalescence.
9	5	Acute	9·16	9·72	9·86	9·35	I	Œdema.
	+1 mth.		9·74	10·26	9·74	9·58	II	Well.
11	8	Acute	11·6	14·1	12·3	10·3	II	Almost well.
12	11	Chronic	4·8	4·9	5·0	6·57	IV	Ill: Chvostek.
	+10 days		4·62	5·0	4·88	5·15	IV	I.S.Q.A.
	+2 mth.		9·24	9·86	9·9	9·52	I	Much improved.
18	1½	Chronic	10·96	13·07	11·14	10·52	II	Œdema.
19	8	Acute	9·43	11·82	9·74	10·08	III	Almost well.
20	7	Acute	9·6	10·76	10·17	9·43	II	7 days after uræmic twitchings.
21	9	Acute	8·7	9·58	8·27	9·35	III	Œdema.
22	5	Acute	6·97	7·6	7·29	8·88	IV	Œdema.
23	9	Acute	8·54	8·54	8·77	8·77	IV	Uræmic convulsions.
	+1 mth.		9·86	10·45	9·4	9·68	III	Well.
24	8	Acute	7·91	8·91	8·7	8·26	I	Œdema.
	+2 wk.		9·27	9·56	9·58	9·0	II	No œdema.
			CONTROLS					
15	7	Colitis	9·71	10·1	10·2	10·0	C	Well.
16	6	Chorea.	10·38	11·41	11·5	10·72	C	Well.
17	6	Bronchitis	9·62	11·05	10·3	10·1	C	Convalescent.
25	9	Rheumatic heart Dis.	8·9	10	9·24	9·08	C	Convalescent.
26	10	Rheumatic heart dis.	9·62	10·95	10·1	10·05	C	Convalescent.
27	10	Rheumatic heart dis.	9·6	10·14	9·86	9·77	C	Convalescent.
28	9	Rheumatic heart dis.	9·76	10·7	9·86	9·86	C	Convalescent.

series but much wider variation in the increase was noted. This becomes more obvious if the control and nephritic figures are contrasted (Table 3).

Since each control curve reached its peak not later than 4 hours, this has been adopted as the maximum time during which comparisons of absorption may be drawn and the average increase in both cases is found to be exactly equal (0·97 mgrm. per 100 c.cm. of serum). In four of the nephritic curves, the maximum increase did not occur until 6 hours, and if these figures be included in the average, the increase in nephritis becomes slightly more than in normal, namely, 1·11 mgrm. per 100 c.cm. of serum.

Of the five nephritic children in whom a poor rise was found after 4 hours, two were the subjects of balance studies (Cases 4 and 8). Although the blood-calcium curves seemed to indicate some defect in absorption, in both a positive CaO balance was found, indicating that the balance cannot be predicted from the type of blood curve. If the rise in the calcium curve is contrasted with the retention of CaO and the percentage of CaO intake appearing in the urine, it will be found that no relationship exists between them. Three children

TABLE 3.

AVERAGE CALCIUM CONTENT OF BLOOD OF NORMAL AND NEPHRITIC SUBJECTS AFTER THE INGESTION OF CALCIUM LACTATE.

Subjects	No. of curves	Ser. Ca. mgrm. per 100 c.cm.			Increase mgrm. per 100 c.cm.		
		Fasting	4 hr.	Increase	% of fasting	Smallest	Greatest
Control	7	9·66	10·63	0·97	10·04	0·49	1·43
Nephritic	28	8·98	9·95	0·97	10·8	0·25	2·87

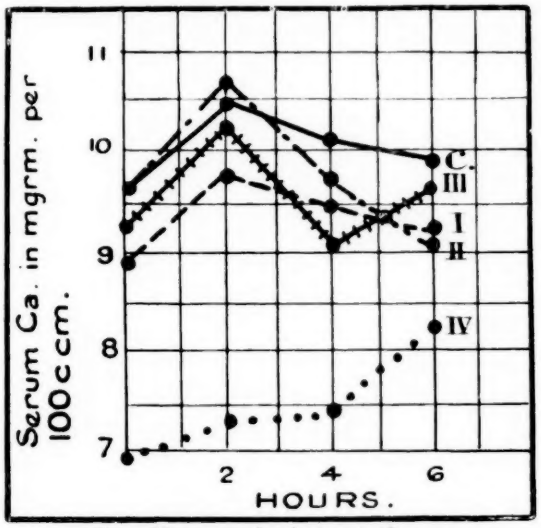
(Cases 11, 8 and 9) gave a negative balance, but the respective blood curves showed increases of 2·5, 1·0 and 0·52 mgrm. per cent. Nor did the highest retention figures correspond with the greatest elevation in the blood curve. Similarly with the urinary excretion, Case 9, while excreting by this route only 1·13 per cent. of CaO intake, showed a rise of 0·7 mgrm. in the blood-calcium curve. Some time later, when the urinary figure had risen to 2·68 per cent., i.e., more than double its previous amount, the calcium curve showed an increase of 0·52 mgrm. per cent. This lack of relationship is shown also by the control subjects in whom both the CaO balance and blood curve were observed.

Cases obtained during different stages of illness, however, show more definite indication of some upset in calcium metabolism during the active stage of the disease with a gradual return to normal as convalescence advances. In each of two children (Cases 5 and 12) three curves were obtained and in six others (Cases 3, 7, 8, 9, 23, 24) two curves. This procedure was suggested by the change in retention found in convalescent children, and also by the altered distribution of the calcium excretion. The increase in serum calcium had no relationship to either the fasting level or the stage of the disease.

Case 12, with fasting estimations, on two occasions, of 4·8 and 4·6 mgrm.per 100 c.cm , showed corresponding elevations of 1·77 and 0·53 mgrm. Similarly Case 5 with primary observations of 7·87 and 9·24 mgrm. per cent., showed on each occasion an increase of 0·89 and 1·07 mgrm. per cent., i.e., an almost identical increase in the height of the two curves. Case 24, with fasting levels of 7·91 and 9·27 mgrm. per cent., gave a greater rise on the first observation (1·0 mgrm.) than on the later one (0·31 mgrm.). In each case the later curves were observed after the onset of definite clinical improvement, and although the increase did not seem to be dependent on the fasting level, yet the type of curve obtained during different stages of the illness showed marked aberration from the normal. This is most easily appreciated when the figures are graphed.

CHART IV.

COMPOSITE GRAPHS OF DIFFERENT TYPES OF SERUM CALCIUM CURVE.



C. = Mean graph of 7 control curves
I. = „ „ 6 Type I „
II. = „ „ 9 „ II „
III. = „ „ 6 „ III „
IV. = „ „ 5 „ IV „

The graphs have been arranged in groups entirely from their general appearance, since no other method of classification could be found. Four categories have been adopted. The average curve of each group is graphically presented in Chart IV.

Type I. Curves very similar to the control curves. This includes two cases of acute nephritis with great œdema ; two cases of acute nephritis during convalescence ; and a convalescent chronic parenchymatous nephritis.

Type II. Curves characterized by the occurrence of a fall in serum calcium at 6 hours of such magnitude that the final reading had fallen below the fasting level. The subjects in whom this was found were one case of acute nephritis ; six acute cases in various stages of convalescence ; one case of renal

dwarfism ; one of functional albuminuria ; and a case of chronic parenchymatous nephritis showing much œdema ten days preceding the onset of a fatal pericarditis.

Type III. Curves in which a good increase was obtained at 2 hours, followed by a marked fall, attaining at 4 hours a level even lower than the fasting, with a subsequent terminal rise at 6 hours. This group also shows some variety in its subjects, namely, one case of acute nephritis with uræmia and some œdema ; two of acute nephritis, one of which had œdema ; two cases of acute nephritis during a rather slow convalescence ; and one late convalescent case.

Type IV. A final group in which a variable increase was found at 2 and 4 hours, with the maximum elevation shown by the 6 hours specimen. The cases falling into this category are :—one child immediately after cessation of uræmic convulsions ; one case of acute nephritis with generalized anasarca ; one of acute nephritis in early convalescence ; one of chronic nephritis which ultimately left hospital comparatively well.

Thus in each group are found examples of the various stages of the disease, with and without œdema, a factor which does not appear to have any constant effect on the behaviour of the calcium curve. If the curves observed in different stages of nephritis are followed, it is found that the one type of curve seldom occurs twice in the same child, suggesting that there is either defective absorption or alteration in the intermediate metabolism of calcium. Examination of the charted curves of other observers does not show variations to have been found in normal subjects similar to those just described in nephritis, and since the average increase in the serum calcium value has been shown to be quite as large in nephritic as in normal children, and also, as will be shown later, the urinary excretion of calcium is invariably diminished, it seems probable that the anomaly lies in the intermediate metabolism of calcium.

In view of these findings it looks as if the low urinary output of calcium in nephritis cannot be the result of an alteration in absorption, and the factors producing it must be sought elsewhere.

(2) **Phosphorus absorption.**—Wigglesworth and Woodrow[20] have shown that in healthy subjects an increase of 55 to 60 per cent. occurred in the inorganic blood phosphorus after ingestion of 25 grm. of acid or alkaline phosphate. They found that the inorganic phosphate was equally distributed between plasma and corpuscles, which means that an increase is present in both and therefore can be determined by estimation of the inorganic phosphorus in the serum alone.

As was the case with calcium two methods of investigating phosphorus have been tried by earlier workers : (1) prolonged administration of phosphorus salts with random blood observations, and (2) serial observations after one dose. The latter method, employed by Murdoch[21] in her study of absorption in normal and rachitic children, seems preferable and was the method adopted in the present work. In each case food was withheld for a minimum period of 3 hours before the fasting specimen of blood was obtained. Four grammes of NaH_2PO_4 dissolved in approximately 100 c.cm. of water were then given, and

samples of blood withdrawn after 1, 2 and 4 hours. Estimation of serum inorganic phosphorus was carried out immediately after each specimen of blood was obtained. During the investigation food and water were temporarily withheld.

Twenty-two blood curves were thus obtained from fifteen nephritic children. Control curves were constructed in ten children convalescent from other diseases, mainly chorea and rheumatic arthritis (Table 4).

The control curves show considerable variation in detail, but closely resemble those obtained by Murdoch[21] in normal children of the same ages, 6 to 12 years. The fasting level varied in different individuals from 4·6 to 6·3 mgrm. per 100 c.cm., i.e., within the normal range. In all, definite increase in the serum inorganic phosphorus was found one hour after administration of the phosphate. In six cases the maximum rise was shown at this time ; in four it occurred at 2 hours, and in one, a case of diabetes, it occurred at 4 hours. At this time, in all but the case of diabetes, the return to fasting level was well advanced, but in none had that level been reached. The increase varied in amount as in the time of attaining a maximum, the range being 0·75 to 3·2 mrgm. per 100 c.cm., and there did not seem to be any relationship between the height of the curve and the fasting level.

In three of the subjects of these control tests balance studies were also carried out, and in these the rise in the curve gave no indication of the retention found. Nor did it indicate the percentage of intake which was excreted by the urine, except that in these three instances, the smaller the increase in the blood curve the higher the percentage excretion by the urine. This might be explained on the assumption that the lower curves indicate a more active renal excretion and occur as a direct consequence of the latter. Such an assumption, however, is not warranted on this small number of observations.

Failure of all these curves to regain fasting level in 4 hours aroused interest, and several curves were prolonged for periods varying up to 14 hours in an attempt to find how long a time would elapse before fasting level was again restored. As will be seen from Table 4, two cases had almost regained fasting level in 13 and 14 hours respectively. A third, falling at 7 hours, rose again, and at 10 hours was higher than at any part of its course. Of the remaining two cases, one was rapidly approaching normal at 7 hours, while the other showed considerable elevation persisting at this time.

Wigglesworth and Woodrow[20] found increase in blood inorganic phosphorus persisting 10 hours after a large dose (25 grm.) of phosphate, in the healthy adult. Not only did it persist, but having reached a maximum elevation in one hour, no decrease was found in frequent estimations made throughout the day. They therefore suggested that phosphate behaves as a threshold substance and is excreted by the kidney only when the blood concentration exceeds a certain undetermined value. This may explain the type of curve found by them, but it does not assist in explaining the slow, more or less steady fall extending over 10 or 12 hours found in the control cases of the present series. Wigglesworth and Woodrow[20], Brain and Kay[22], and Salvesen[23] have all found marked increase in urinary excretion of phosphorus after elevation of the blood phosphorus has been induced either by oral or intravenous administration of phosphate.

The ability of the normal kidney to excrete much more than the customary amount cannot therefore be questioned and one is forced to conclude that the

TABLE 4.

SERUM INORGANIC PHOSPHORUS OF NEPHRITIC AND CONTROL SUBJECTS AFTER INGESTION OF NaH_2PO_4

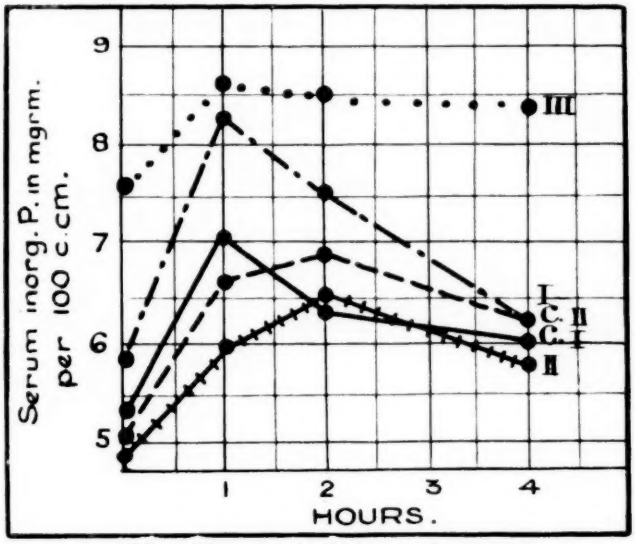
Case No.	Age in years	Nephritis	Serum inorg. P. in mgrm. per 100 c.cm.				Type of graph	Stage of disease
			Fasting	1 hr.	2 hr.	4 hr.		
1	11	Acute	6·66	9·23	8	6·85	I	Convalescent.
3	12	Acute	6	8	7·5	6·3	I	In acute stage.
	+5 mth.		5·21	7·5	7·06	6	I	Almost well.
4	13	Chronic	12	12·63	12·63	12·63	III	Very ill; œdema.
5	9	Acute	4·8	5·71	6·48	5·71	II	Convalescent.
7	10	Acute	6	7·06	7·06	6·66	III	Convalescent.
8	6	Acute	5	6·31	7·06	6·31	II	Early convalescence.
	+1 mth.		4	6·66	5·21	4·44	I	Late convalescence.
9	5	Acute	7·06	8·88	8	8·27	III	Just after uræmia.
	+1 mth.		4·8	6·48	6·48	5·6	I	Well.
11	8	Acute	4·6	4·7	5·3	5	II	Convalescent.
12	11	Chronic	12	13·33	13·33	13·33	III	Very ill.
	+2 wk.		9·23	10	10	9·6	III	I.S.Q.A.
	+2 mth.		6·15	7·27	7·27	7·27	III	Much improved.
19	8	Acute	4·28	5·45	5·58	5·1	II	Convalescent.
20	7	Acute	5·21	6·81	7·31	6·15	II	Early convalescence.
21	9	Acute	8·57	12	10·8	8·9	I	In acute stage.
22	5	Acute	4·9	6·15	5·71	6	III	Œdema.
23	9	Acute	4·89	6	6·48	6·31	III	Just after uræmia.
	+1 mth.		5·1	6	6	5·6	III	Well.
24	8	Acute	5·66	6	6·31	5·85	II	Œdema.
	+2 wk.		5·15	6·85	7·5	6·85	II	Improving.
			CONTROLS					
15	7	Colitis	6·31	8·16	6·86	6·66	C.I	Well.
16	6	Chorea	4·8	8	7·7	6·6	C.I	Well.
17	6	Bronchitis	5·85	8	8·57	7·4	C.II	Convalescent.
25	9	Rh. arthritis	5·33	7·06	6·41	5·85	C.I	Convalescent.
26	10	Rh. arthritis	4·61	5·71	5·85	5·33	C.II	Convalescent.
29	12	Chorea	5	7·06	6·48	6	C.I	Convalescent.
27	10	Rh. arthritis	5	5·48	6·31	—	C.II	Convalescent 14 hr. 5·21 mgrm.
28	9	Rh. arthritis	5·71	7·06	6·31	—	C.I	Convalescent 13 hr. 5·77 mgrm.
30	7	Chorea	4·7	5·45	5·1	5·02	C.I	Convalescent 7 hr. 5·2 mgrm. 10 hr. 5·6 mgrm.
31	8	Chorea	5	6·31	6·66	5·85	C.II	Convalescent 7 hr. 5·45 mgrm.
14	6	Diabetes	4·61	6·66	6·85	7·06	—	7 hr. 5 mgrm.

effect of high blood phosphorus content on the general metabolism is not such as to demand its urgent removal even in normal persons.

In fifteen nephritic subjects very similar results were obtained (Table 4, Chart V). The fasting level varied between 4 and 12 mgrm. per 100 c.cm., nine being over 6 mgrm. In 13 curves the maximum rise occurred at 1 hour, and in all it had been reached by 2 hours. Again, there was great variation in the amount of increase, the range corresponding to that of the control series, and as in the latter, no relationship could be found between the fasting level and the height of increase in the curve. This is well illustrated in Case 12, from whom three curves are available for study. The first, observed during an acute exacerbation of a chronic nephritis, showed a fasting level of 12 mgrm.

CHART V.

COMPOSITE GRAPHS OF DIFFERENT TYPES OF P. SERUM CURVE.



C.I. = Mean graph of 6 control curves
C.II. = „ „ 3 „ „
I. = „ „ 6 nephritic „
II. = „ „ 7 „ „
III. = „ „ 9 „ „

and a rise of 1·33 mgrm. per 100 c.cm. The second, in early convalescence, showed the fasting level to be 9·2 and the rise 0·8; while the third, some time later, had a fasting level of 6·15 and a rise of 1·1 mgrm. per cent.

Nor could the phosphorus curves be correlated with the clinical condition. Case 12, on three occasions, showed the same type of curve; a maximum rise attained at 1 hour, and remaining steady at 4 hours. Improvement in his renal function, which had undoubtedly taken place, was not accompanied by a more rapid fall in the blood curve, and in view of the type of curve found by Wigglesworth and Woodrow[20] this cannot be labelled an abnormal curve.

Similarly presence of œdema was apparently of no significance so far as the phosphorus curve was concerned. Case 4 with generalized œdema showed a curve similar to those found in Cases 12 and 23 which had no œdema. Case 22

and Case 1 with marked œdema showed curves which were alike but different from the above, and also from the third type of curve shown by another œdematous subject, Case 24.

On the whole, the nephritic curves compared very favourably with normal curves from the point of view of absorption. Even when the fasting inorganic phosphorus was around 12 mgrm. per 100 c.cm., a state of affairs generally regarded as indicative of death within a few weeks, there was definite evidence of absorption. It will be seen from Table 5 that the average fasting level, highest level attained, and increase in the control subjects are in absolute agreement with Murdoch's normal curves. In the nephritic subjects the fasting levels, when averaged, are higher, as are the maximum elevations; but the increase is not quite so great, being about 25 per cent. lower. The range, however, is very similar in the control and nephritic cases of this series.

Defective absorption, as judged by the curves, cannot be held responsible for the lowered P_2O_5 balances observed in the repeated studies (Tables 1 and 4). Case 3 on each occasion showed an increase of 2 and 2·29; Case 8, 2·05 and

TABLE 5.

AVERAGE SERUM INORGANIC PHOSPHORUS CONTENT OF NORMAL AND NEPHRITIC SUBJECTS AFTER INGESTION OF NaH_2PO_4.

Subjects	No. of curves	Ser. inorg. P. in mgrm. per 100 c.cm.			Smallest increase	Greatest increase
		Fasting	Highest	Increase		
Murdoch's	3	5·3	7·1	1·8	1·6	2·2
Control	9	5·25	7·05	1·8	0·75	3·2
Nephritic	22	6·22	7·58	1·36	0·65	3·43

2·65; and Case 9, 1·8 and 1·7 mgrm. per cent. In the other case it was not possible to determine an earlier phosphorus curve, but the one obtained during the second balance period showed an increase of 1·7 mgrm. per cent.

Comparison with the P_2O_5 retention figures and with the percentages of intake excreted by the urine shows that there is no correlation between these and the rise in phosphorus curve. Case 8, with a minimal retention of P_2O_5, showed the highest rise in the curve (2·65 mgrm., i.e., well above the average normal rise of 1·8 mgrm.), and in Case 4 the rise in the curve was 0·65 mgrm. and the retention adequate. The urinary figures showed similar confusion, and the inverse relationship shown by the three control curves was not found in nephritis.

Summary of blood calcium and phosphorus findings.

1. The average rise of the calcium curve in nephritic subjects is equal to that found in control subjects, but the average rise of the phosphorus curve in nephritic subjects is lower than that of controls.

2. The height of the rise in both the calcium and phosphorus curves is independent of the fasting level both in nephritic and normal subjects.

3. The duration of the rise of both the calcium and phosphorus curves in the nephritic subjects is more variable than in the normal cases.

4. None of the types of calcium and phosphorus curves could be found to bear any relationship to the clinical condition of the cases.

5. The height of the calcium and phosphorus curves bore no relationship either to their urinary output or their retention.

III. EXCRETION OF CALCIUM AND PHOSPHORUS IN NEPHRITIS.

(1) **Urinary excretion.**—Reference has already been made to the fact that for many years diminution in urinary excretion of calcium and phosphorus in nephritis has been generally recognized.

This has been observed repeatedly, but the first significant work on excretion of calcium by the nephritic kidney seems to have been done by Hetenyi and Nogradi[24] in 1925. In order to avoid any difficulty arising from variations in absorption, they injected intravenously 10 per cent. solution of calcium chloride, and found that in uræmia the urinary calcium output increased very slightly in the two hours following injection. Even in patients convalescent from acute nephritis, the urinary excretion rose less than half the amount found in normal subjects, showing that, whatever the cause of the impairment of renal excretion, some time elapsed before the kidney recovered its excretory power. In common with others, they failed to find in nephritis, in marked contrast to the normal, any increase in urinary calcium excretion following increased intake.

Boyd, Courtney and McLachlan[3] concluded that the nephritic kidney was incapable of excreting calcium in normal fashion as evidenced by the low total excretion and by the low concentration in the urine. With regard to phosphorus, they were of opinion that in nephritis urinary excretion compared favourably with normal.

Thus, while all previous workers are unanimous in the opinion that there is low renal output of calcium in nephritis, some doubt has been expressed as to whether the phosphorus output is also diminished. In the present investigation eleven cases of nephritis were examined, four of them on two occasions, and the figures for urinary excretion show that, without doubt, the quantities of calcium and phosphorus voided by this route were subnormal (Table 1). Before discussing these in detail, it is necessary to consider the normal urinary output of these elements.

Holt, Courtney and Fales[7], while studying the calcium metabolism of normal children, indicated that the main source of recovery of the surplus calcium intake was the fæces. Findlay, Paton, and Sharpe[25], Telfer[26], Sherman and Hawley[5] agree with this finding, placing the urinary calcium at from 1 to 12 per cent. of the intake. MacRae[6], working in this laboratory with children under 12 years, has found that the urinary output of calcium represents on the average 6·74 per cent. of the intake, and the control subjects of this series showed a similar distribution, 4·7 to 7·6 per cent. of intake.

As regards urinary phosphorus, Sherman and Hawley's figures ranged between 44 and 64 per cent. and both Telfer's and MacRae's averaged around 50 per cent. of the intake in normal children. The control subjects of this investigation excreted from 33 to 49 per cent. of intake in the urine.

It appears, then, that there is considerable variation in the urinary excretion, even in normal children. The average percentage of intake recovered from the urine approximates to 6 per cent. for CaO, and 50 per cent. for P_2O_5.

The figures in the nephritic subjects show very definite variation from the

normal. The average amount of calcium in the urine, for all 15 balance experiments, whether in the acute stages, during convalescence, or in the chronic forms of the disease, was 2·02 per cent. of the intake. The maximum output for the series was that shown by a chronic case, 3·9 per cent. of intake, i.e., well below the average of 6 per cent. in health. In no instance of acute nephritis did the urinary calcium output exceed 3 per cent. of intake, while in one subject it was found to be only 0·94 per cent.

Of the four repeated balance observations, there was apparent in three definite improvement in renal excretion of calcium at the time of the second observation (Table 6). In the fourth case the first period was observed during a phase of extreme diuresis which followed an attack of acute uræmia complicating a bronchiectasis. No satisfactory explanation for the decreased excretion during the later balance period could be found.

The behaviour of the urinary phosphorus was found to be roughly parallel to that of the calcium. From the average urinary content expressed in terms of intake it seems that the decrease is not so marked as in the case of calcium. The average fraction of phosphorus intake appearing in the urine was 32 per cent. as compared with the normal average of 50 per cent. Thus while only one-third of the normal quantity of calcium appeared in the urine more than half the normal amount of phosphorus was excreted by this route. It was noted that the range of urinary phosphorus excretion was smaller than in healthy children, being with one exception between 26 and 43 per cent. of the intake. The lowest figure, 8·4 per cent. of intake, was shown by a case of chronic nephritis shortly before a fatal pericarditis. The maximum urinary excretion of phosphorus did not occur in the child who showed the maximum calcium excretion. In fact, in all forms of nephritis there was evident more defect in the excretion of calcium than of phosphorus although even the latter only approached the normal proportion in two subjects, one of whom was convalescent.

Here, as in the case of calcium, the four repeated balance observations showed that urinary excretion of phosphorus had improved in the second period (Table 6). It was found that Case 5, which showed a decreased output of calcium, had a slightly increased urinary phosphorus, demonstrating again that there is no absolute parallelism between the two.

As was indicated in the section on calcium and phosphorus utilization, no relationship could be traced between the retentions and the figures for urinary excretion (Charts III and IV). Likewise the urine volume was not found to have any bearing on the quantitative excretion of calcium and phosphorus.

With one exception, previous workers on the serum phosphorus in nephritis have accepted the theory of defective excretion by the kidney. That there is justification for this is shown when the serum and urinary phosphorus contents are compared (Chart III). The lowest urinary phosphorus of the present series occurred in Case 4, which showed the highest serum level. Serum values within normal limits, however, did not indicate a normal distribution of the phosphorus excretion, and one must therefore conclude that although a high

serum inorganic phosphorus may occur coincidently with a low urinary output of phosphorus, yet they are not directly interdependent. Looking at the urinary calcium excretion from the same point of view it is evident that with the lowest serum values there is found the lowest excretion (Chart II). But again, normal serum values do not foretell a normal urinary excretion of calcium and thus it seems, as in the case of phosphorus, that the renal output is not directly dependent on the serum level.

(2) **Fæcal output.**—In healthy children the proportions of calcium and phosphorus intake excreted in the fæces are fairly constant. From Sherman and Hawley's[5] figures it has been calculated that the fæcal portion of the total phosphorus excreted averaged 37·7 per cent. MacRae's[6] figures for normal children showed an average of 40 per cent. in the fæces, of the total phosphorus excreted; while the control cases of the present series gave an average of 43·5 per cent. Thus in 22 normal children the fæcal phosphorus amounted to an average of 39·2 per cent. of the total output. If this be expressed in terms of intake it appears that 30·3 per cent., i.e., about one-third, of the ingested phosphorus is eliminated by the bowel.

When corresponding calculations are made for the cases of nephritis it is evident that 62·3 per cent. of the excreted phosphorus is present in the fæces. There is, therefore, a relative increase in the fæcal content. If this be expressed in terms of intake, it is found that an average of 54·2 per cent., i.e., more than half, of the ingested phosphorus appears in the fæces, showing that there is also an absolute increase in fæcal content in nephritis.

A similar aberration from normal is evident in the fæcal excretion of calcium. The average fæcal content in healthy children was found to be 91 per cent. of the total output, representing 64·7 per cent., or almost two-thirds of the intake. In nephritic subjects these figures were increased. A larger portion of the total output, averaging 97·4 per cent. appeared in the fæces, thereby accounting for 78 per cent., or more than three-quarters of the intake. Thus, an increase, relative and absolute, is found in both the calcium and phosphorus contents of the fæces, of which the increase in phosphorus is relatively the greater.

This inequality of increase is more easily appreciated if the CaO to P_2O_5 ratio be considered. In MacRae's[6] normal children and in the control series of the present study considerably more CaO than P_2O_5 was present in the fæces. The ratio in these subjects averaged 1·34 : 1. When the nephritic figures are examined, it is found that the fæcal CaO and P_2O_5 contents were more nearly equal, the average ratio being 1·08 : 1.

The four repeated balance studies (Table 6) seem to show that these abnormalities have some significance since they approached normal as convalescence proceeded. In one patient (Case 3) after an interval of four months, analysis showed increased output of calcium and phosphorus in the urine, decrease in the fæcal content, and rise in the CaO to P_2O_5 ratio. Balance studies repeated in three other subjects at shorter intervals showed that the urinary phosphorus increased in three, the urinary calcium in two, and fæcal CaO to P_2O_5 ratio in all three. The intestinal output of both calcium and

phosphorus, however, had increased to such an extent that negative balances were found, and it is worthy of mention that the only other negative balances were found in children during early convalescence, along with abnormally high fæcal output, low urinary excretion, and low CaO to P_2O_5 ratio in the fæces. From this it would seem that the upset in calcium and phosphorus metabolism in renal disease is not confined to the more acute stages of the disease, but persists for some weeks after convalescence has begun.

TABLE 6.

COMPARISON OF THE FÆCAL AND URINARY EXCRETIONS IN THE ACUTE AND IN THE CONVALESCENT STAGES OF NEPHRITIS.

	Fæcal CaO as % of intake	Urine CaO as % of intake	CaO retention per kgrm. per day	Fæcal P_2O_5 as % of intake	Urine P_2O_5 as % of intake	P_2O_5 retention in grm. per kgrm. per day	Ratio fæcal CaO to fæcal P_2O_5
Case 3.							
Acute stage	6·85	1·8	·054	49·1	27·8	·058	1·01
4 months later; late convalescent	62·7	3·5	·048	40·7	33·8	·053	1·04
Case 5.							
Acute stage	49·6	2·7	·042	37·7	31·7	·038	0·94
1 month later; convalescent	73·2	1·7	·023	55·3	32·5	·014	1·01
Case 8.							
Acute stage	75·2	2·3	+·025	57·1	30·3	·017	1·10
5 weeks later; convalescent	107·3	3·25	—·013	62·1	37·6	·0003	1·17
Case 9.							
Acute stage	96·3	1·13	+·033	66·0	33·6	+·0008	1·04
3 weeks later; convalescent	98·4	2·68	—·0017	69·2	42·5	—·0225	1·06

Summary of the results of experiments in urinary and intestinal excretion of calcium and phosphorus.—1. The excretion by the urine of both calcium and phosphorus is diminished in nephritis, the calcium excretion being diminished to a greater extent than the phosphorus.

2. The amounts of calcium and phosphorus excreted in the urine by nephritic patients bear no relationship to their respective retentions nor to urine volume.

3. The fæcal output of calcium and phosphorus is increased in nephritis.

4. The increase in the phosphorus excretion by the bowel is greater than that of calcium, the normal CaO to P_2O_5 ratio being reduced almost to unity.

5. The process of restoration of the normal route of excretion is extremely slow and is delayed for some time after the onset of convalescence.

General conclusions.

Studies of the retention, absorption and excretion of calcium and phosphorus in nephritis indicate that :—

(a) retention is not abnormally high ;

(b) absorption, though more variable than normal, is adequate ;

(c) there is a deviation of both calcium and phosphorus excretion from the urine to the fæces.

I have pleasure in expressing my thanks to Dr. Leonard Findlay for affording me facilities for the study of the clinical material and for much helpful advice ; also to the Carnegie Trust for their financial assistance.

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TWO CASES OF DOUBLE URETER

BY

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Pyuria in childhood has been the subject of a good deal of recent attention. The older conception of acute pyelitis as an inflammatory condition confined to the pelvis of the kidney has been questioned by Chown and others, who have brought forward evidence to show that in such patients the kidney substance is involved at least as much as its pelvis. Congenital abnormalities of the urinary tract are now recognized to be frequent causes of continued pyuria in childhood and recourse to cystoscopy, pyelography and intravenous urography is quite properly advised when there is a failure to respond to medical treatment. Co-operation between physician and surgeon is never more necessary than in the unravelling of the causes of chronic pyuria in children. Abnormalities of the urinary tract may preclude independent existence or limit it to a matter of days. Occasionally, an abnormality defies even the precise methods of present-day urology and is only discovered post mortem.

Case reports.

The two following cases illustrate some of the difficulties. In both children the deformity was of the same kind. In the first patient death occurred at the age of 25 days ; in the second, pyuria lasted from the age of three months to three years but, in spite of previous investigation, its cause was only determined after three hours of dissection post mortem.

Case 1.—The first patient was a male aged ten days who was admitted to hospital for enlargement of the abdomen which had been noticed at birth and had even caused difficulty during labour. Physical examination showed a large, firm swelling occupying the right loin, while a smaller mass was palpable in the left iliac fossa. The urine contained albumin and pus. The infant was so weak that further investigation was impossible and, after a short downhill course. He died at the age of twenty-five days. The illness was not accompanied by fever, vomiting or convulsions.

At post-mortem examination the only abnormality was in the urinary tract. The right kidney consisted of a large hydronephrotic sac the size of a fœtal head and the kidney tissue was only one to two millimetres thick (see Figure 1). The right renal pelvis consisted of two portions, each draining into its own ureter ; the right ureter was thus double. One of these ureters was straight and opened into the bladder in the usual position. The other was dilated and twisted; the lower end was prolapsed into the bladder with the orifice of the ureter placed at the summit

of the prolapsed portion. The left ureter was normal and opened normally into the bladder. The left kidney was slightly swollen and an early pyonephrosis was thought to be present. The bladder was displaced into the left iliac fossa by the huge right kidney and accounted for the tumour palpated in that position during life. The urethra was normal.

Case 2.—The second case was a girl (shown at the Children's Section of the Royal Society of Medicine, for Dr. J. H. Thursfield[1]) who first came under observation in May, 1930, at the age of three years. At three monthly intervals since the age of twelve weeks she had had attacks of fever accompanied by the passage of turbid urine.

On examination at the age of three years she weighed 27 lb. and appeared fairly healthy. The urine was cloudy, alkaline, and containing much pus; bacillus coli was grown from it. The blood urea was 44 mgrm. per 100 c.cm. Cystoscopy showed the presence of severe cystitis but

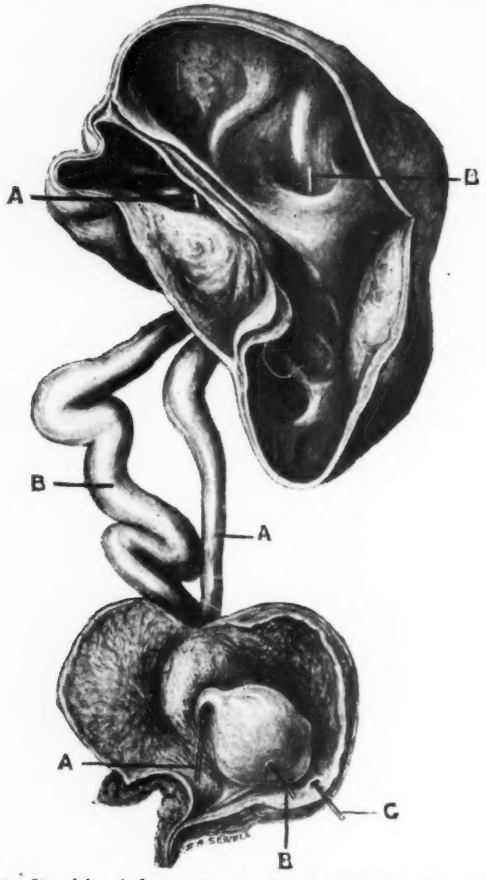

FIG. 1. Case 1. Double right ureter and pelvis from a boy aged ten days. The two right ureters are labelled A and B. C is the vesical orifice of the normal left ureter. (Half natural size).

no other bladder abnormality. A ureteric catheter entered the left ureter without difficulty, and the pyelogram showed a greatly dilated and somewhat tortuous ureter. Several attempts to catheterize the right ureter failed, the catheter buckling each time after entering two or three centimetres. Eventually a successful passage was made and the resulting pyelogram showed a normal right ureter and renal pelvis. 35 ccm. of 40 per cent. uroselectan was then given intravenously and could be seen by X-ray examination to have entered the left renal pelvis and left ureter. It was not, however, visible in the right pelvis or ureter. A cystogram was then taken by filling the bladder with sodium iodide solution (13·5 per cent.) and raising the buttocks. The opaque solution ran upwards into the left ureter and clearly outlined it: none entered the right ureter.

The interpretation of these results was difficult and largely conjectural. The evidence seemed to show that the left ureter was more dilated than the right and that its lower end was incompetent. On the other hand, although the right kidney apparently did not secrete uroselectan, yet direct pyelography after considerable difficulty in passing the ureteric catheter showed a seemingly normal pelvis and ureter. The left kidney and ureter were thought to be primarily at fault and it was decided that an operation should be performed on that side in the hope of eliminating the area of disease.

On January 1st, 1931, the left kidney was exposed by operation. It was slightly enlarged and the ureter dilated to about half an inch in diameter. The left kidney and the first three

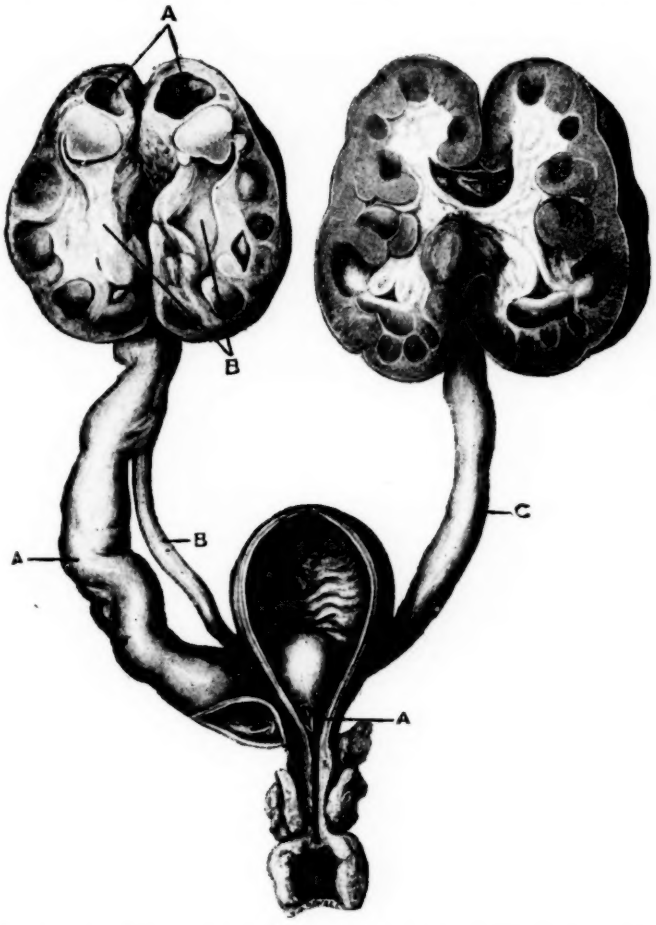

FIG. 2. Case 2. Urinary tract from a girl aged two years and ten months. The ureter and pelvis are double on the right side and the two portions are labelled A and B. C is the single left ureter (Half natural size).

inches of the ureter were removed, but on opening the kidney it was seen that its structure did not depart much from the normal. Microscopically, there was a slight invasion of the interstitial tissue with small round cells, but otherwise the components of the kidney were normal. The child remained well for 48 hours after operation but the temperature then rose to 102°F. A small quantity of pus was evacuated from the wound. The patient, however, remained ill, vomited and became drowsy. Partial suppression of urine followed and the child died on the fifth day after operation, apparently of uræmia.

At post-mortem examination the only abnormality lay in the urinary apparatus. It was at once obvious that, contrary to expectations, the right ureter was dilated and very tortuous.

The whole of the urinary tract was removed en bloc and the subsequent dissection proved very tedious. Eventually, it became clear that the right ureter was duplicated, both portions being bound within a common sheath. One of the ureters was considerably dilated, measuring about an inch in diameter; the other was of normal calibre but followed the tortuosities of the dilated one. The ureteric catheter had evidently entered the smaller ureter and the difficulty in passing it was no doubt due to the tortuosity. On opening the right kidney a few drachms of purulent urine escaped. The pelvis was in two separate compartments. The larger part of the kidney drained into the lower and larger pelvis which communicated with the smaller ureter (see B, Figure 2). The upper half of the pelvis consisted of a small pyonephrosis, surrounded by a narrow, tough ring of kidney tissue, and drained into the dilated right ureter (see A, Figure 2). The small right ureter opened into the bladder opposite the left ureter and in the usual situation. The dilated right ureter, however, continued down to the neck of the bladder. From a bulbous termination a minute passage turned at right angles to traverse the muscular wall of the bladder. Here it entered a chamber beneath the mucous membrane of the bladder close to the beginning of the urethra. This chamber could be distended to the size of an acorn with fluid and at its lower end there was a tiny slit-like orifice which opened into the bladder in the mid-line just proximal to the vesical sphincter. Both orifices were only large enough to admit a bristle. It is possible that the submucous chamber should be called a ureterocele of the dilated right ureter. The urethra was normal.

The right kidney on microscopic examination showed a heavy infiltration with small round cells. The glomeruli were in places adherent to their capsule and the vessels were slightly thickened. The piece of tough kidney surrounding the pyonephrosis at the upper pole of the kidney showed advanced fibrosis and disorganization. Only a few glomeruli could be made out and they were atrophic, while the few tubules that were present were dilated. The vessels in this area showed a severe degree of thickening due to endarteritis.

Figure 2 is a drawing from the case. It will be noted that the left kidney is shown in continuity with the ureter, though actually the kidney had been removed five days before death. The post-mortem examination throws some light on this case but it is uncertain whether or not the submucous chamber was dilated during life. During cystoscopy the bladder is necessarily distended with fluid and this clearly collapsed the chamber and made it invisible. Moreover, the minute mid-line orifice was so near the vesical sphincter that the cystoscope passed over it before the field became illuminated. Possibly a small cysto-urethroscope might have demonstrated the abnormality, had its exact position ever been suspected. Uroselectan might have solved the problem by indicating the double right ureter, but, for some reason not clear to us, the drug did not appear in the right kidney.

We wish to express our thanks to Dr. F. J. Poynton and Dr. J. H. Thursfield by whose courtesy we are able to record these cases; to Dr. Lucas for kindly examining the microscopic sections of the kidney; and to Mr. Sewell for his drawings.

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THE INCIDENCE OF UNDULANT FEVER IN CHILDREN

BY

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In the decade since Bevan[1] suggested that the organism responsible for contagious abortion in cattle might be pathogenic for man, innumerable cases of undulant fever have been diagnosed among the populations of most civilized countries. During 1925, there were only 24 cases reported in the United States, but each succeeding year thereafter an increasingly large number was reported until, in 1929, there were more than 1,300. Complete statistics for 1930 are not yet available, but it is safe to assume that there were many thousands of cases. There is every reason to believe that this increase is only apparent, and not real, as cases are being reported now which could not have been recognized before the present methods of laboratory diagnosis came into general use. In the United States at least, the number of cases reported from any given region seems to depend more on the alertness with which the physicians search for the disease than on any other factor.

With the increasing appreciation of the ubiquity and gravity of this disease, it seems advisable for students of children's disease to try to evaluate the importance of undulant fever among the diseases of childhood. Several theoretical considerations suggest that a higher incidence of infection prevails among children than among adults. The Brucella abortus causes a low-grade, febrile illness of a type which is frequently undiagnosed unless specific laboratory tests are made. Such low-grade fevers are so much more common in children than in adults that it would seem reasonable to expect a higher incidence of Brucella infection among children than among adults when specific tests are generally applied. Also the fact that raw milk customarily constitutes a large part of the diet of infants and little children suggests that infection may be found to be common in childhood. Despite these considerations, it has become the more or less tacit opinion of writers on undulant fever that the disease is relatively uncommon in children. In fact, some authors have gone so far as to argue that Brucella infection is not caused by drinking milk because children seem to contract the disease so infrequently in spite of drinking large quantities of milk.

Previous investigations.—In 1913, Larson and Sedgewick[2] tested 425 children with bone or joint disease for complement fixation, using Brucella abortus as antigen. This test was positive in 73 instances. At that time, it was not known that this organism could act as one of the human pathogens. These studies were carried out as a part of a problem relating to the transmission of antibodies through the intestinal wall. Nothing is said about the ages of the children nor about the probable source of the infection. Later these same workers[3] used the

same test on 42 new-born babies, with negative results. One baby was taken from the breast on his 7th day, because of high fever, the cause of which was never ascertained. He was then fed on raw cows' milk. On his 21st day his reaction was positive. Another baby, 19 months old, had a positive reaction.

In 1915 Nicoll and Pratt[4] raised the question of human infection with Brucella. They performed agglutination tests on an unstated number of the inmates of a foundling asylum, including cases of marasmus, rickets, enlarged lymph nodes, and hypertrophied tonsils and adenoids, as well as on about 100 supposedly normal infants. Presumably these patients were getting raw milk. One 3 year old child had a positive reaction to 1 : 100; one child of 2½ years had a slightly positive reaction to 1 : 10; a 5 year old child had a positive reaction to 1 : 10. Otherwise they were all negative. These same writers also found a positive reaction in the 7 months old baby of a woman whose own serum reaction was positive in dilutions up to 1 : 300.

Hardy[5], in summarizing all cases of undulant fever reported in the United States up to June of 1929, found very few instances in children under 10 years of age. Among 354 cases in Iowa, this author noted only 4 in children under 4 years, and 8 in children between the ages of 5 and 9 years. Of these, 6 were in one family, the diagnosis being made on the basis of dried blood specimens alone. His data were collected chiefly from various State laboratories and consequently are not very useful in an attempt to determine the incidence of the disease among children. Most of the blood specimens submitted to such laboratories come from rural practitioners who rarely take blood specimens from young children. Extensive bacteriological and serological studies of the blood of young children are very infrequently made save in city clinics where, of course, the general use of pasteurized milk precludes the satisfactory study of Brucella infection. The same criticism applies to the statistics of Bayne-Jones[6] who found no positive agglutinations in infants under one year in some 3,700 routine blood specimens on which Brucella agglutination tests were made in the New York State laboratory. In similar specimens in the Ohio State laboratory, Ey[7] found positive agglutination reactions in one child of 19 months, in whose family there were three persons sick with undulant fever; and in another child of 2 years who was sick with an undiagnosed febrile illness.

In Denmark Kristensen[8] has made a careful study of 500 cases of undulant fever and concluded that young children are not affected. Guest[9] carried out agglutination tests on 250 patients in the Children's Hospital of Boston, and found only one who reacted positively in dilutions up to 1 : 40. He does not state whether these children used raw or pasteurized milk. Giordano and Sensenich[10] have reported 35 cases, the youngest being 16 years old. Hartman[11] mentions an infection occurring in an 8 year old child. Bonynge[12] had a case in an 11 months old infant who had been using certified milk for 9 months. Three other children in the same family had been using this milk but were not affected. King[13] noted four cases in children under 6 years of age, including one 2 year old child who had what was believed to be rheumatic fever until a chance agglutination against Brucella was found to be positive in dilutions up to 1 : 1280. This child, however, had been transfused with blood from two adults who had agglutinins in their sera. Simpson[14] studied 90 cases of undulant fever, nine of which occurred in children between the ages of 6 and 10 years. Kling[15], in Sweden, found only one case under 10 years, a child of 8 years. Levin[16] made intradermal tests on 33 children between the ages of 6 months and 14 years. Only one child, a 5 year old girl with sinusitis and mastoiditis, gave a positive skin reaction. Her serum did not contain Brucella agglutinins. Kohlbry[17] saw the disease in an infant of 1 year The diagnosis was made on the basis of positive agglutination test done three days after the baby was transfused with its mother's blood. Koschate[18] considers childhood infection to be so rare that he reports the case of a 12 year old boy as a curiosity. Tobler[19] has reported Brucella infection in an 8 year old girl.

Present investigations.—Since the literature on the occurrence of undulant fever in childhood is so fragmentary and inconclusive, it seems worth while to record any item which may be helpful in the understanding of it.

In the autumn of 1930 a small epidemic of undulant fever appeared in a school community which uses raw milk from a single dairy. Several moderately severe cases of the disease occurred among the adult milk consumers. Of some

300 adolescent boys and young adults using this milk, 41 per cent. showed serum agglutinins for Brucella abortus in dilutions over 1 : 20. Several of the cows in the dairy were found to have positive sera, and some were shedding virulent organisms in their milk. Among the consumers of this heavily infected milk, were fifteen children who had been reared on this raw milk since infancy. The age distribution of these children was as follows :—

Under 1 year	1
1—2 years	3
2—4 ,, ...	4
4—6 ,, ...	4
6—8 ,, ...	2
8—10 ,, ...	1

At least three agglutination tests, each with a different antigen, were done on each one of these children. The first antigen was a stock one made from four strains of Brucella of bovine origin ; the second, the so-called Huddleson antigen ; the third, a live antigen prepared from a strain of Brucella isolated from the blood of a patient[20] who was infected through drinking the same raw milk which the children used. The dilutions in these agglutination tests were from 1 : 10 to 1 : 640. In not one of these children could any Brucella agglutinins be demonstrated. All of these children had been under the continuous care of the writer either since their birth, or at least for the two years preceding the testing. In that time, none of them had any illness which could possibly be suspected of being undulant fever. Although this series is very small, the results seem to justify the supposition that young children are less susceptible to infection with Brucella than are persons who have passed puberty

In this connection, it is tempting to speculate on the apparent analogy between Brucella infection in young children and in calves. White[21] states that all calves, regardless of the reaction of the dams, are born non-reactors.. When they are permitted to suck positive dams within the first 24 hours of life, they become reactors in a remarkably short time, but again become negative, almost invariably before the end of the sixth month of age. It is only after sexual maturity that definite infection is established.

Summary.

A review of the literature of undulant fever shows that little is definitely known regarding the infection in childhood.

Study of serum agglutination in young children, who had been drinking infected raw milk, suggests that they are relatively insusceptible to the disease.

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[EDITORIAL NOTE. So far two cases only of Brucella infection in children have been reported in England: the first in a child of 3½ years by W. Broadbent, *Lancet*, Jan. 10th, 1931: the second by B. Williamson and J. Gibson in a child of 1⅞ years, *B.M.J.*, May 2nd, 1931.]

FAMILIAL SPLENIC ANÆMIA

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The three cases, the notes of which are given in full, are of particular interest in that they are in members of one family.

Case reports.

Case 1.—Robert D., aged 14 years, was admitted to hospital in June, 1925. Nine months previously he had several attacks of hæmatemesis. A good recovery was made and he was apparently in good health until a few days before admission, when he complained of pain in the abdomen. Splenic enlargement was discovered, and he was admitted to hospital for investigation and treatment.

The boy was well developed for his age; there was slight pallor of the mucous membranes, and the lower border of the spleen was felt three inches below the costal margin.

TABLE I.

BLOOD IN CASE 1.

Blood examination :—	per c.cm.	per cent.
Red cells	4,100,000	
Hæmoglobin	70	
White cells	1,800	
Polymorphonuclears	540	30
Lymphocytes	1,116	62
Eosinophils	108	6
Transitionals and mononuclears	36	2

Fourteen days after admission splenectomy was done by Mr. E. H. B. Milsom.

At operation it was noted that there was slight enlargement of the liver, but there was no evidence of cirrhosis. The spleen was considerably enlarged, weighing 25 oz., and showed perisplenitis. It had a purplish colour and was doughy to palpation. The splenic vein was not thrombosed. Microscopic examination showed a generalized fibrosis, less in degree than in the subsequent cases. There was marked endothelial proliferation in the Malpighian bodies. No eosinophils were seen.

Recovery from the operation was uneventful, and the boy was discharged from hospital in 21 days.

Six months later he had a further hæmatemesis, and on admission it was found that the liver was enlarged and there was well marked ascites. His red cells numbered only 1,840,000 per c.mm. Under treatment the ascites cleared and the blood picture improved.

After 13 months, during which time he was working, he had a further hæmatemesis, came into hospital, developed a mesenteric thrombosis and died.

POST-MORTEM EXAMINATION.—There was deep jaundice. There was thrombosis of mesenteric veins, with gangrene of the greater part of the ileum and generalized peritonitis,

The liver was enlarged and smooth and weighed 3¼ lb. There was no cirrhosis. The portal vein was thrombosed. The stomach showed multiple small erosions throughout the mucous membrane. There was no varicosity of the œsophageal veins. A small accessory spleen was found to show the same changes as the spleen.

Case 2.—Edith D., aged 15½ years, admitted December, 1928, had been in good health until the previous day, when she had complained of abdominal pain. During the night she had vomited blood on several occasions.

On examination there was marked pallor of skin and mucous membrane. The spleen was palpable about two inches below the costal margin. There was no ascites.

TABLE 2.

BLOOD IN CASE 2.

	per c.mm.	per cent.
Red cells	3,020,000	
Hæmoglobin		55
White cells	3,630	
Polymorphonuclears	2,540	70
Lymphocytes	982	27
Transitionals	108	3

Fragility of red cells	normal.
Wassermann reaction	negative.
Bleeding time...	4 minutes.
Coagulation time	5 ,,
Blood group	Type III.

Splenectomy was performed by Mr. Kenneth Mackenzie on January 24th, 1929, and the girl was discharged well four weeks later. At operation the liver was not enlarged; its surface was smooth; it appeared normal. The spleen weighed 22 oz., showed perisplenitis and generalized fibrosis. Microscopically the Malpighian bodies were much diminished in number: those remaining were much encroached on by fibrous tissue. Eosinophils were abundant. In parts there was great dilatation of sinuses which were filled with blood.

During the next six months, the patient had two attacks of melæna, which were controlled by intramuscular injections of whole blood. After an operation for removal of septic tonsils, at which there was no undue bleeding, she remained in perfect health for 14 months. She appeared a particularly robust and well developed girl. Menstruation was regular and never excessive.

On October 21st, 1930, her blood count showed:—

Red cells	5,500,000 per c.mm.
Hæmoglobin	90 per cent.
Platelets	495,000 per c.mm.

One month later, she complained of faintness, passed black stools, and vomited bright blood several times. In spite of repeated transfusion, she died within 36 hours from the onset of symptoms. The blood platelets at this time numbered 240,000 per c.mm.

POST-MORTEM EXAMINATION.—The œsophagus contained blood. The veins at the lower end of the œsophagus, and the adjacent part of the stomach were varicose, but their walls appeared to be intact.

The stomach contained a large quantity of blood. The mucous membrane appeared quite healthy, and there was no evidence as to the source of the hæmorrhage. The intestines contained much blood. There was marked hæmolytic staining of the mucosa of the distal part

of the small intestine and in the proximal half of the colon. There was no thrombosis of mesenteric vessels. Several mesenteric glands were enlarged and caseating. The liver was of normal size, but very pale. There was no thrombosis of the portal vein, and no cirrhosis. There were no spleniculi, and the other organs were essentially normal.

Case 3.—Ronald D., aged 11½ years, was admitted to hospital on August 9th, 1929. The boy's health had been good until the night before admission, when he vomited blood several times.

On examination there was marked pallor and slight fever (100·6°). The tonsils were enlarged and septic, though not acutely inflamed. The liver and spleen were not palpable, and there was no demonstrable ascites. Red blood cells numbered 2,440,000 per c.mm., and there was 40 per cent. of hæmoglobin. Three days later, the spleen was just palpable below the costal margin, and there were definite signs of ascites. One week after admission, although there was no further hæmorrhage, anæmia was increasing. The spleen now was found to extend two inches below the costal margin, and there was more fluid in the abdomen.

The condition of the blood on August 16th is shown in Table 3.

TABLE 3.

BLOOD IN CASE 3.

	per c.mm.	per cent.
Red cells	1,912,000	
Hæmoglobin		30
White cells	2,200	
Polymorphonuclears	1,300	59
Lymphocytes	792	36
Transitionals	88	4
Eosinophils	22	1
Platelets	104,000	

Wassermann reaction	negative.
Fragility of blood cells	normal.
Blood group	Type III.

Under treatment, the blood picture improved, and the fluid was absorbed from the abdomen. The spleen gradually increased in size, and anæmia persisted. On June 12th, 1930, he had slight melæna, and it was decided to remove the spleen.

This was done by Mr. Kenneth Mackenzie a few days later. The spleen weighed 15 oz. Perisplenitis was present. On section the spleen was of uniform brownish colour, and doughy to feel. Microscopically there was a general fibrosis of the whole organ, with disappearance of normal spleen pulp and of many Malpighian bodies. Eosinophils were numerous.

Six months after the operation, the boy was in much better health and growing rapidly. His red blood cells were 4,000,000 per c.mm., hæmoglobin 80 per cent., and platelets 304,000 per c.mm. Tonsillectomy was performed and some septic teeth removed without undue bleeding.

He remained in good health until February, 1931, when bleeding recurred, and while in hospital mesenteric thrombosis brought about his death. While active hæmorrhage was taking place his platelets numbered 260,000 per c.mm.

POST-MORTEM EXAMINATION.—There was a mesenteric thrombosis with gangrene of six feet of ileum. There was a large quantity of blood in the small intestine. The splenic vein was thrombosed. The stomach contained no blood. There were small erosions in the mucosa. The vessels of the œsophagus showed no varicosity. The liver was very fatty. There was no cirrhosis, and the portal vein was not thrombosed. No spleneculi were found.

Other members of the family.—The mother of the children was a particularly healthy woman, and her family history and that of the father were quite negative.

The mother's blood reacted negatively to the Wassermann test. The other members of the family, a girl Edna, aged 20, and James, aged 13, were examined, and no splenic enlargement was found. There was no history of hæmorrhage in either case.

Blood examination of the two unaffected children showed :—

	Edna.	James.
Red cells	4,200,000 per c.mm.	5,040,000 per c.mm.
Hæmoglobin	80 per cent.	90 per cent.
White cells	10,420 per c.mm.	7,000 per c.mm.
Polymorphonuclears	49 per cent.	44 per cent.
Lymphocytes ...	42 ,, ,,	49 ,, ,,
Transitionals ...	7 ,, ,,	4 ,, ,,
Eosinophils ...	2 ,, ,,	3 ,, ,,
Platelets	147,000 per c.mm.	166,000 per c.mm.

Discussion.

Osler[1] defined splenic anæmia as 'a chronic affection characterized by progressive enlargement of the spleen, which cannot be correlated with any known cause as malaria, leukæmia, syphilis, cirrhosis of the liver, etc. ; a marked tendency to hæmorrhage, and in many cases a terminal stage with cirrhosis of the liver, jaundice and ascites.'

This definition is a wide clinical one, and includes conditions of totally different pathology. Banti's disease is now known to be a separate entity, as is the syndrome described by Wallgren, thrombosis of the splenic vein.

In spite of advances made in clinical and pathological knowledge, the term 'splenic anæmic' as generally used, still includes conditions differing in their clinical manifestations, and probably in their pathogenesis. Tidy[2] in discussing the hæmorrhagic diathesis, has stressed the difficulty of separating some cases of splenic anæmia from the hæmorrhagic diathesis. The cases described fall into this category. A thorough search of the literature available has failed to discover any record of cases of splenic anæmia, or of any similar clinical syndrome occurring in members of one family.

Apart from the question of diagnosis, there are many interesting features in these cases. The hæmorrhagic state was intermittent. In between attacks, the children were in good health, and there was no tendency to hæmorrhage, for instance, after tonsillectomy or tooth extraction. Blood platelets were normal in number, even during a period of active bleeding. Splenic enlargement did not precede, but was subsequent to the first hæmorrhage. Splenectomy had no effect in preventing the onset of the hæmorrhagic state.

In the case of Ronald (Case 3), recovery after the first severe hæmorrhage appeared to be slow in comparison with the other two who had the spleen removed. However, when his splenectomy was done later, his blood condition improved.

In no instance did the operation of splenectomy appear to make any difference to the ultimate result, the period between the onset of the disease and death being about two years in each case.

TABLE 4

BLOOD EXAMINATIONS BEFORE AND AFTER SPLENECTOMY.

Case No.	Date	Red cells	Hb %	Leucocytes	Polymorphs %	Lymphocytes %	Transitional %	Basophils %	Eosinophils %	Platelets	Remarks
1	15 : 6 : 25	4,100,000	70	1,800	30	62	0	2	6	—	—
	2 : 7 : 25										Splenectomy
	8 : 7 : 25	5,000,000	70	14,000	65·5	25	7	·5	2	—	—
	24 : 7 : 25	4,850,000	75	10,200	27·5	51·5	11	4·25	5·75	—	—
	7 : 8 : 25	5,440,000	75	12,400	24	55·25	9	3·75	8	—	—
	17 : 2 : 26	1,840,000	40	8,800	20	70	8	0	2	—	Bleeding
	13 : 4 : 27	2,480,000	40	15,000	77·5	20	2·5	0	0	—	Bleeding
	19 : 4 : 27	2,208,000	40	16,600	48	42	3·5	1·5	5	—	—
	27 : 4 : 27	2,400,000	40	14,800	67	25	4·5	2	1·5	—	—
2	31 : 12 : 28	3,020,000	55	3,630	70	27	3	0	0	—	—
	22 : 1 : 29	4,870,000	70	2,400	67	26	3	·5	3·5	—	—
	24 : 1 : 29										Splenectomy
	28 : 1 : 29	3,300,000	65	22,000	75	21	3	0	1	—	—
	5 : 2 : 29	4,900,000	70	13,200	64	27	2	1	6	—	—
	12 : 2 : 29	4,930,000	70	11,200	49	37·5	2	·5	11	—	—
	23 : 5 : 29	2,900,000	50	11,400	37	48	2	1	12	—	Bleeding
	13 : 6 : 29	4,900,000	70	7,000	37	46	10	0	7	—	—
	21 : 10 : 29	5,500,000	90	8,800	33	58	3	1	5	495,000	—
	19 : 11 : 29	2,368,000		15,000						240,000	—
3	9 : 8 : 29	2,440,000	40	11,500	69·5	25·5	4·5	·5	0	—	—
	16 : 8 : 29	1,912,000	30	2,200	59·5	36	4	0	·5	—	—
	26 : 8 : 29	2,248,000	35	3,400	64	32	2	0	2	—	—
	30 : 8 : 29	2,600,000	40	3,300						104,000	—
	26 : 9 : 29	3,712,000	50	2,000	40	60				—	—
	19 : 6 : 30	5,000,000	75	4,800	43	48	4	0	5	—	—
	25 : 6 : 30										Splenectomy
	6 : 7 : 30	4,500,000	75	14,400	61	25	5	·5	8·5	1,000,000	—
	27 : 7 : 30	4,800,000	70	16,000	64	29	5	0	2	600,000	—
	21 : 10 : 30	4,000,000	80	14,400	34	52	6	0	8	304,000	—
	13 : 2 : 31	3,936,000	55	14,400	68	29	3	0	0	260,000	Bleeding

It is obvious that the pathological process must have been the same in each case, and it is difficult to understand why two of the patients should develop mesenteric thrombosis, whilst the third should die from hæmorrhage, apparently due to increased capillary permeability—seemingly diametrically opposed conditions.

The series of blood counts given in Table 4 are of interest, as showing the changes that occurred in the blood picture following splenectomy.

As shown in the accompanying table the alterations in the blood picture after splenectomy are :—

1. Well-marked and maintained increase of leucocytes.
2. Sudden rise of platelet count, followed by gradual fall to normal limits.
3. Slight increase in eosinophil cells.

Summary.

Three cases of splenomegaly associated with the hæmorrhagic diathesis are described in a sister and two brothers.

The term ' splenic anæmia ' is tentatively applied to the condition.

Splenectomy was done in all three cases, and appeared not to affect the course of the disease.

My thanks are due to Dr. W. Gilmour, Director of the Pathological Laboratory of the Auckland Hospital for reports on the pathological material, and for his co-operation in the preparation of this paper.

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A CASE OF PERFORATED DUODENAL ULCER IN AN INFANT

BY

L. PRISCILLA HARRISON, M.B., B.S.

(From the Royal Free Hospital, London.)

The following case of perforated duodenal ulcer in an infant is reported, not only on account of the rarity of the condition, but also because the symptoms and course presented differ somewhat from those in previously reported cases.

Peptic ulcers are evidently not very rare in infants under one year of age, but only a few have been recorded in England. In Welch's[1] collection of 607 cases of peptic ulcer only one occurred under ten years of age. Koplik[2] reported one case of peptic ulcer out of 300,000 cases of diseases of children, and Rokitansky[3] stated that he never saw a case under fourteen years. In 1926 Theile[4] collected 248 cases of peptic ulcers in children; 138 of these occurred in the first year, and one-third of the entire series in the first month of life; 58 per cent. were duodenal and 42 per cent. gastric. Altogether, duodenal seem to occur more frequently than gastric ulcers. In 364 autopsies under one year Entz[5] found ten duodenal and only one gastric ulcer. Females are more commonly affected than males.

The age incidence seems to correspond to that of marasmus. Holt[6] in 65 cases noted that 70 per cent. occurred between six weeks and five months.

Perforation.—Although over 200 cases of duodenal ulcer in infants have been recorded in the literature, only nine cases of perforation have been found. Nevertheless, Adler[7] remarks on the large percentage of perforations which occur in acute ulcers in children.

The following have each reported one case of perforated duodenal ulcer in infants under one year: Borland[8], Adriance[9], Finny[10], Helmholz[11], Griffith[12], Schmidt[13], and Somerford[14]. Entz[5] has recorded two instances.

Case report.

T.L., a female infant, born on December 25th, 1930, was admitted to the Royal Free Hospital under the care of Dr. Chodak Gregory on Feb. 24th, 1931. The child had been born three weeks premature by instrumental delivery. She was the second child in the family. Birth weight 8½ lb. She had been breast fed 3-hourly from birth, and had been treated at Moorfields Hospital for ophthalmia neonatorum.

At 9.0 p.m. on February 22nd, the baby suddenly started to scream and draw up its legs. Similar attacks followed in quick succession. Next morning at 4.0 a.m. the mother noticed that the abdomen was distended. This distension steadily increased. There was no vomiting; the stools were perfectly normal and the baby continued to take well.

On admission the temperature 96°, pulse 130, and respirations 40. The baby was markedly wasted, only weighing 7 lb. 2 oz. The face was pale and drawn. The anterior fontanelle was large and depressed, the posterior fontanelle still present, the occipital and frontal bones some what bossed and the sutures too prominent. The palate was high and narrow, the eyes slanted

vertically especially the right, and both showed scars of ophthalmia neonatorum. Some nasal discharge was observed.

The abdomen was tense and distended and the umbilicus unfolded (Fig. 1). Dilated veins were seen in the upper part of the abdominal wall. There was no visible peristalsis, nor were any organs palpable on account of the distension. The percussion note, although tympanitic, was impaired in the flanks, but no shifting dullness or fluid thrill was detected. The liver dullness was normal: nothing abnormal was found on rectal examination.

The distension of the abdomen rapidly increased and the abdominal wall became tense and shinys and finally œdematous and red. Œdema also appeared in the scalp.

The baby continued to take well; there was no vomiting at any time, the stools were normal in colour but relaxed, four to nine motions being passed daily, and there was no melæna. The child slept well and did not cry, although the face always wore an anxious expression.

The temperature remained normal throughout, with the exception of the second day after admission when there was a temporary rise to 101·4°.

On March 4th the abdomen was explored as signs of free fluid had developed; the resulting fluid on examination appeared to consist of contents of the small intestine.

FIG. 1. Condition 4 days after admission. Note the extreme distension of the abdomen; also the dilated veins.

Just before death the circumference of the abdomen decreased from 17·2 in. to 16·5 in.

The child died on March 5th, eleven days after the onset of the symptons, at the age of ten weeks.

Investigations.—Nasal swab. Friedlander's pneumobacillus was found to be the predominating organism on culture. No gonococci were seen. The Wassermann reaction and Kahn test were negative. Fluid withdrawn from peritoneal cavity. Direct film showed very degenerate cells, numerous large gram-positive sporing bacilli, some gram-negative bacilli and a few gram-positive cocci in short chains. On culture there were B. coli, B. welchii, and anærobic streptococci. Chemical examination of the fluid showed that bile was present, also trypsin and fat. The diastase index was over 50, showing the presence of pancreatic secretion and therefore suggestive of the contents of the small intestine.

Post-mortem examination.—A wasted child with a very distended abdomen, on opening which some gas escaped. The peritoneal cavity was found to contain yellowish fluid, also some curdy material of a similar colour, evidently stomach contents mixed with bile, lying anteriorly to the stomach and left lobe of the liver. On breaking down adhesions the jejunum and ileum

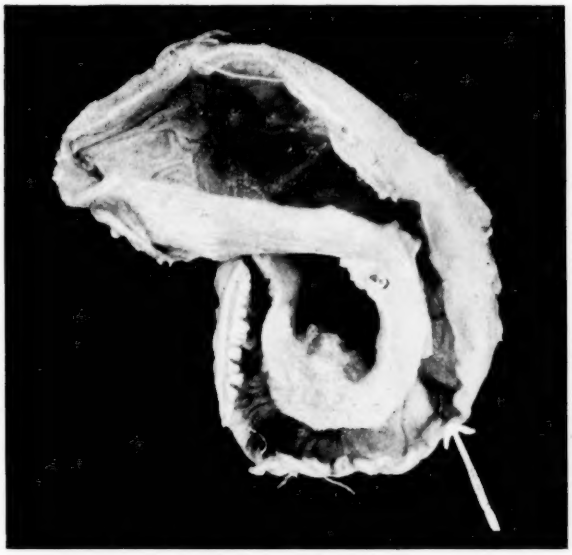

FIG. 2. Stomach laid open to show the hypertrophy of the musculature. The ulcer is denoted by arrow.

were found to be normal. An ulcer about ½-inch in diameter was found just distal to the pylorus on the posterior wall of the duodenum (Fig. 2). The edges of the ulcer were over-hanging, the base showed no perforation and was not very indurated, but the appearances suggested that the ulcer had perforated and had subsequently healed. There was considerable hypertrophy of the pyloric musculature and also of the stomach wall. Another small acute ulcer was present in the pyloric region of the stomach. The other organs showed no changes of importance.

Microscopically the ulcer showed rolling of the mucous membrane at the margins. The floor consisted of the muscle coat covered by a thin layer of granulation tissue. Extension by

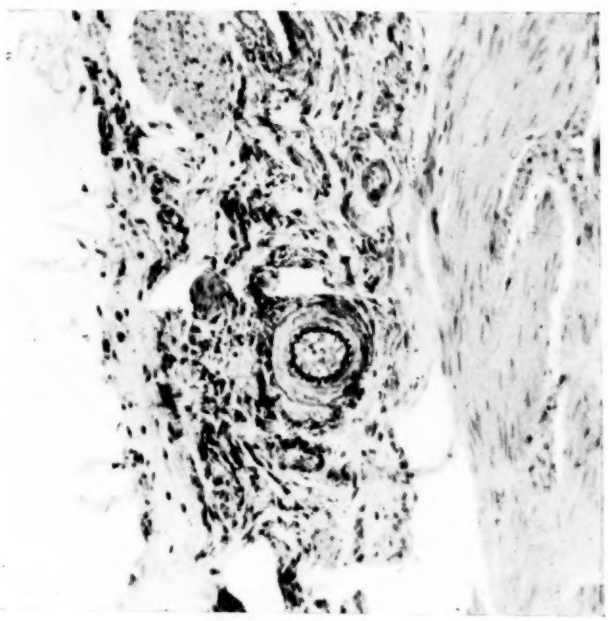

FIG. 3. Microphotograph of the base of the ulcer. Note vessel showing complete obliteration of the lumen by proliferation of intima. Stained Weigert's elastic stain and hæm-alum and eosin.

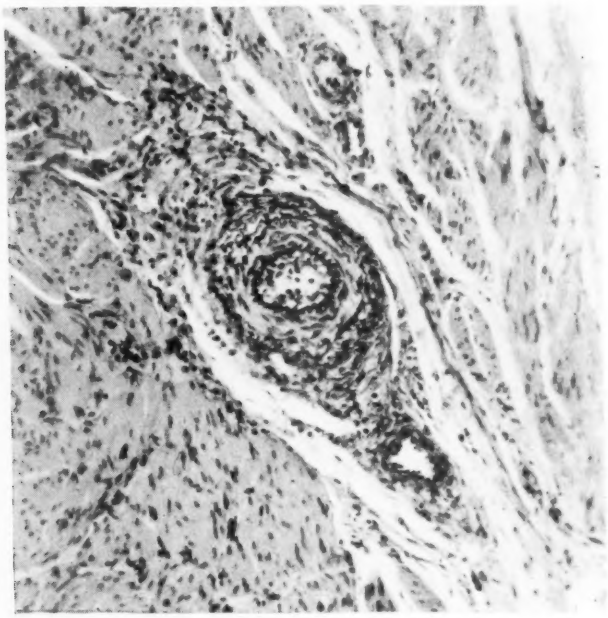

FIG. 4. Microphotograph of vessel showing active stage of endarteritis. Intima shows proliferation. Several lymphocytes can be seen in the newly formed tissue. Stained Weigert's elastic stain and hæm-alum and eosin.

necrosis was going on in the submucous coat at the margins. There was much cellular granulation tissue between the muscle bundles which was fairly well preserved. Several vessels in the base of the ulcer showed recent thrombosis, and the small arterioles in the subperitoneal layer showed active peri- and end-arteritis (Figs. 3, 4 and 5). The vascular change was much more striking than that usually found in peptic ulcers.

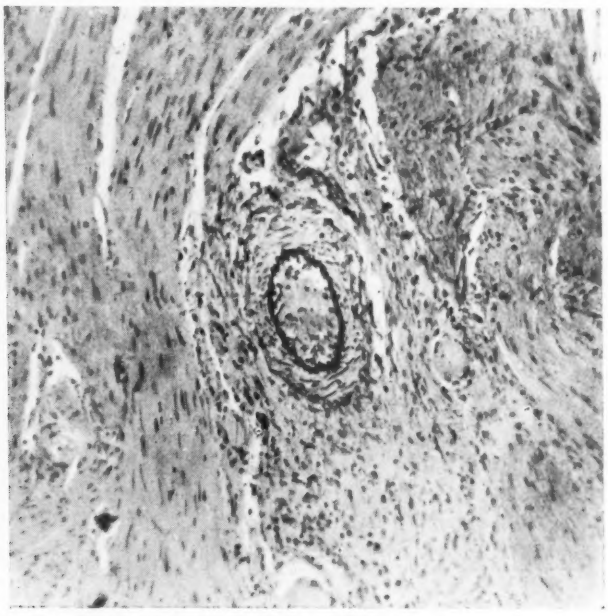

FIG. 5. Vessel in muscle coat under floor of ulcer, showing thrombosis and early recanalization. Stained Weigert's elastic stain and hæm-alum and eosin.

Ætiology.—Study of the literature suggests that the causes predisposing to peptic ulceration are lowered general vitality and previous digestive disturbance. Vascular changes seem to be of chief importance as a determining cause, a small hæmorrhage being followed by gastric digestion of the infarcted area. Shore[15] groups the causes of vascular disturbance into congestion, embolism, thrombosis, direct vascular injury and diseases of the nervous system. Other ætiological factors which have been suggested are: prenatal disposition (Jacobi[16]), tuberculosis, hyperacidity, bacterial necrosis, burns (Paterson[17]) and anatomical abnormalities (Rogers[18]).

Peptic ulcers which have caused no definite symptoms during life are sometimes found at post-mortem examinations of marasmic infants. The large majority of these ulcers are single and it is very rare to find more than three in any one infant.

In the present case microscopic examination showed definite vascular lesions which may justifiably be regarded as the direct cause in initiating the peptic digestion of the devitalised mucosa.

Situation.—Duodenal ulcers are always found to be above the papilla of Vater on the posterior wall of the duodenum, and just below the pyloric ring.

The ulcer is usually punched out. Both round-celled infiltration and induration are uncommon. Holt[6] has observed that this condition is quite often associated with pylorospasm and congenital pyloric stenosis.

Symptoms.—It has been stated that the symptoms may be absent singly or collectively, or may be latent. Perforation and subsequent peritonitis often give rise to the first symptoms, death usually occurring in less than 36 hours. According to Holt[6] one-third of all cases give no symptom of ulcer.

Hæmatemesis and melæna are the most characteristic symptoms. Other cases show continual vomiting and gastro-intestinal symptoms. On examination there are commonly pain and tenderness in the epigastrium.

In the case described death did not supervene until eleven days after the ulcer perforated. Hæmatemesis and melæna were both absent, nor was there any vomiting. The child did not cry on palpation of the epigastrium.

Summary.

1. A case of duodenal ulcer in a female infant, aged 10 weeks, is described.

2. There is no doubt that the ulcer had perforated, probably on February 22nd, and that before death the perforation had closed. This is perhaps the most remarkable feature of the case.

3. The afebrile course is probably explained by the fact that the duodenal contents escaping into the abdominal cavity were nearly sterile and the peritonitis set up was non-infective, being due to the mechanical irritation caused by the presence of food.

4. The absence of melæna is probably due to the fact that the vessels in the floor of the ulcer were no longer patent, only a few capillaries retaining their lumen.

5. In this case marked endarteritis and periarteritis occurred in the vessels supplying the ulcerated area.

My thanks are due to Dr. Chodak Gregory for allowing me to use the notes of this case and for her invaluable help and advice; also to Dr. Ross for the photographs and pathological reports.

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ENURESIS OF ALLERGIC ORIGIN

BY

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Persistent enuresis is a common complaint, difficult to eradicate and obnoxious to all concerned, whether patient, parent, or physician. It is not my desire, in this preliminary communication, to recapitulate the multitudinous ætiological factors nor discuss the numerous recognized therapeutic aids in this condition, but rather to expand an observation which I made in an article on the asthmatic child which appeared in this journal last year[1]. In this I stated that, in my experience, a few cases of persistent enuresis in children were allergic in origin. The cases to which I referred may be classed into three categories :—First, cases in which enuresis occurs along with such allergic manifestations as asthma, hay-fever, eczema, urticaria and migraine ; secondly, cases in which enuresis is present along with conditions that have proved allergic in origin ; thirdly, cases in which enuresis occurs as the sole manifestation of allergy.

Parents of young allergic children are loath to admit that the child wets himself as they regard it as an infantile weakness that will soon disappear at the age of seven or puberty. They are always more concerned with the asthma or other allergic complaint that has commenced recently and which, in their view, is liable to persist throughout life. It is only in the case of older children that the statement is volunteered, for they have been distracted to find that the habit did not cease with the second dentition. In a thousand allergic children I have found that 5 per cent. over the age of seven years suffer from some degree of enuresis.

If we compare the nerve supply of the bladder with that of the lungs the reason for the association between enuresis and such an allergic condition as asthma becomes obvious. For just as constrictor fibres are supplied to the smooth muscle in the walls of the bronchi through the cranial division of the parasympathetic system, motor fibres are supplied to the detrusor muscle of the bladder and inhibitory fibres to the internal vesical sphincter through the sacral division of the same system. On the contrary, the bronchi are dilated through sympathetic fibres inhibiting their smooth muscle, and the internal sphincter of the bladder and the trigonal region are contracted and the detrusor muscle inhibited through a similar innervation. Obviously stimulation of the parasympathetic system may lead to bronchospasm, or to the discharge of urine, or both, according to the location or intensity of the stimulus, whilst any endeavour to stimulate the sympathetic to counteract the asthmatic tendency may lead, in addition, to the cessation of a bed-wetting habit.

Clinical evidence supports this suggestion, for one of the distressing effects of ephedrine in some patients is to lead to an inability to micturate due to a spasmodic constriction of the vesical sphincter.

The analogy between enuresis and allergic conditions in general does not cease with the similarity in innervation of the affected organs. Both conditions tend to occur in bouts with intervals of comparative freedom, both tend to be worse at night, both tend to be accentuated by fatigue or worry probably due to sympathetic exhaustion, and both commonly clear up on admission to hospital.

First, the cases in which enuresis is associated with other evidences of allergy are frequent. The sensitizing proteins may be foods, animal emanations or physical agents either singly or in combination. In some cases the same protein causes both the enuresis and other allergic reaction, whilst in other cases different proteins are concerned.

W.S., a boy aged five years, had always wet the bed. For three months he had had asthmatic attacks each week-end, which were always preceded by intense stomach-ache and accompanied by more frequent lapses. In spite of fluid restrictions, the administration of belladonna, and waking at specified intervals, the habit continued unabated. Skin tests revealed a hyper-sensitivity to wheat, and forced feeding of wheaten foods over several days always brought on the stomach-ache and enuresis. Since the rigid restriction of wheaten foods eighteen months ago neither the asthma nor the enuresis have reappeared.

B.C., a boy of eleven years, had suffered from enuresis always and from asthma every three weeks for the past four years. His maternal grandmother suffered from asthma. He gave huge skin reactions to feathers and rabbit hair which comprised his bedding, and their removal led to a cessation of both complaints.

P.L., a boy aged three years, suffered from facial eczema, asthma, and enuresis. There was a strong family history of allergy on the mother's side. The boy gave positive skin reactions to feathers, horsehair, egg, pork, potato and rice, the removal of which relieved all symptoms.

Secondly, in some cases enuresis accompanies other conditions that have proved allergic in origin.

C.C., a girl of three and a half years, had wet the bed since birth, and for the past eighteen months had had several severe crops of lichen urticatus. The child's maternal grandmother suffered from asthma. Positive skin reactions were obtained to pork, and by eliminating all pork, bacon and lard from the diet four months ago the child has not wet the bed once nor have any more spots appeared.

Besides lichen urticatus, enuresis frequently appears during recurrent colds and persists during the illness. Many of these recurrent bronchitic attacks are allergic in origin and due to a hyper-sensitiveness to feather or horsehair bedding, or in spring and summer colds to pollen hyper-sensitiveness which generally passes unrecognized.

These observations in definite cases of allergy suggested the investigation of some cases in which persistent enuresis was the sole complaint. Many older children who had suffered for several years from this habit and who had been treated in the outpatient department of the hospital for many years with dietary and fluid restrictions and large doses of belladonna without avail, and in whom no urinary abnormalities could be detected, were investigated, and three cases out of fifteen responded to the elimination of substances giving positive skin reactions.

R.P., a girl of ten and a half years, had suffered from diurnal and nocturnal incontinence since birth without intermission. All the boys in the father's family had suffered from enuresis. She had been under constant medical care for some years without any response to the usual therapy. She was found hyper-sensitive to oatmeal, potato, rice and feathers, and since the elimination of these factors a year ago there has not been a wet bed.

The types of case quoted could be amplified[2], but the few chosen serve to illustrate the point that I have endeavoured to stress, namely, that some cases of persistent enuresis are allergic in origin. In cases of this complaint which fail to respond to the routine therapy of waking, fluid restrictions and belladonna the protein skin tests may indicate a causal factor, and its elimination, possibly combined with judicious doses of ephedrine, will probably lead to a prompt cessation of the habit.

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BRITISH PÆDIATRIC ASSOCIATION.

PROCEEDINGS OF THE FOURTH ANNUAL GENERAL MEETING.

The Fourth Annual General Meeting was held at the Abbey Hotel, Great Malvern, on Friday and Saturday, June 12th and 13th, 1931.

FIRST SESSION (JUNE 12TH, 10 A.M.).

Business Proceedings: The President, Dr. Robert Hutchison, was in the Chair, and there were present 47 members.

President: Dr. F. John Poynton was elected President for the year 1931–32, and the Secretary was instructed to write to him expressing the regret of the members at his illness and wishing him a speedy recovery. The election of Officers and Ordinary Members followed, as recommended by the Executive Committee.

Secretary: Dr. Donald Paterson (re-elected).

Treasurer: Dr. Morley Fletcher (re-elected).

Representative Committee Member for London: Dr. Eric Pritchard, in place of Dr. R. C. Jewesbury, who retires under Rule 4.

Representative Committee Member for Ireland: Dr. Brian Crichton, in place of Dr. Rowland Hill, who retires under Rule 4.

Ordinary Members: Dr. A. C. Hampson of London, Dr. Alan Moncrieff of London, and Dr. A. V. Neale of Birmingham.

Next Meeting: The following places were suggested for next year's meeting: Windermere, Ilkley, Llandudno, Harrogate, Gleneagles, Newcastle (Co. Down). Owing to a complaint from the members from the North of the distance which they had to travel to the meeting, it was generally felt that the meeting should be held further North for their convenience in future.

Treasurer's Report: Dr. Morley Fletcher presented the Treasurer's Annual Report, which was adopted. This showed a balance of £72 19s. 9d.

Change of Rules: Dr. Leonard Findlay's motion to increase the membership of the Association to 75, seconded by Dr. Still, was put to the meeting and defeated. His second motion to insert a rule after Rule 16 that 'An Ordinary Member who is absent from three consecutive General Meetings shall cease, ipso facto, to be a member of the Association' was unanimously adopted.

'Save the Children' Union: It was agreed by the meeting that Dr. Schlesinger should represent the British Pædiatric Association at the 'Save the Children Union' meeting at the Hague in September, and that ten guineas should be allocated towards his expenses.

Scientific Communications.

1. DR. F. LANGMEAD (London): 'The role of hæmolytic streptococci in the causation of arthritic purpuras.' He said that the evidence available at the present time pointed in his opinion to increased permeability of the capillaries as the essential precursor of purpura, and he instanced in favour of this contention the association of urticaria and the investigations of Sir Thomas Lewis. Thrombocytopœnia was not a necessary factor, for purpura might occur without it, and thrombocytopœnia might be severe and yet no purpura supervene. Bedson had produced experimentally thrombocytopœnia, but no purpura resulted until an endothelium-destroying serum was also injected. Moreover, the various kinds of so-called primary purpura merged into each other, and in some of them a low blood-platelet count was customary, but in others not.

If it were granted that increased permeability of the capillaries was essential, there remained the question as to the cause of this 'micro-trauma.'

The object of the communication was to indicate that infection by hæmolytic streptococci provided a cause, and to suggest that in treating cases of 'iidopathic' purpura, a search should be made for these organisms, and any focus of infection by them treated as radically as practicable. Dr. Langmead cited four cases in support of this view, two of them corresponding to the clinical description of Schönlein's disease, one to that of Henoch's purpura, and one to purpura simplex. In all a focus of infection by hæmolytic streptococci had been found, treat-

ment of which had been followed by satisfactory results, which strengthened the belief that the streptococci were the cause of the maladies.

2. Dr. K. Tallerman (London): 'Abdominal manifestations in rheumatism.' He said that although it was still open to question whether rheumatism could give rise to symptoms simulating appendicitis, or whether appendicitis or peritonitis could at times be actually caused by rheumatic infection, the cases reported in his communication would appear to be in the former category, since only slight pathological change was noted in the appendices removed at operation. The question was brought forward of whether abdominal pain, occurring without other symptoms in childhood, might in some cases be rheumatic in nature.

3. Dr. Leonard Findlay (London): 'The incidence of the rheumatic infection.' He said that although several writers, e.g., Newsholme in 1895, Poynton in 1920, Miller in 1923, and Glover in 1930, had all stated that the rheumatic infection was diminishing in frequency, he held that the facts were not before us on which to express an opinion. These various authors had based their conclusions on the diminishing proportion of examples of the infection in several London hospitals, but it must be borne in mind that factors other than mere frequency of a particular disease governed admissions to hospital. Dr. Findlay recorded a recent experience in Glasgow in that while the proportion of examples of tuberculous meningitis in hospital was steadily increasing the total number of deaths from this cause in the city as a whole was steadily diminishing. No cause could be assigned to such an occurrence. At any rate in Glasgow since 1875 there was no lessening in the proportion of the examples of the rheumatic infection in either of the general hospitals (Western and Royal Infirmaries) or in the children's hospital, and from the frequency with which heart disease complicated those examples met with in the children's hospital there would seem to be no apparent diminution in the gravity of the disease.

4. Dr. Bernard Schlesinger (London): 'A study of the sleeping pulse rate.' He gave the results of his investigation on this subject. In apyrexial cases he pointed out the fallacies of taking the day or alert pulse rate alone as a true indication of activity of the disease in a child with a rheumatic heart lesion. Such observations disregarded the nervous factor which was often such a marked feature in rheumatic children. Tables and charts were shown of the alert and sleeping pulse rate in normal children, cases with quiescent rheumatic hearts, and those with active carditis. These demonstrated that in healthy children over the age of five years the average difference in the rates was about ten beats per minute. In infants the difference was not so marked. Children with quiescent heart lesions showed the same slowing of the pulse during sleep, but those with obvious active carditis did not. Dr. Schlesinger said that in his experience either a sleeping tachycardia or a pulse chart which showed little difference between the alert and sleeping rates was an indication of active rheumatic carditis. Tachycardia by day accompanied by the usual drop at night when asleep indicated a nervous origin and treatment in bed could then safely be relaxed.

5. Dr. Stanley Graham (Glasgow): 'The value of alkali in salicylate administration.' He said that the administration of sodium salicylate alone produced an acidosis of the non-gaseous type. This acidosis could be prevented by the addition of alkali to the salicylate, but not by glucose. Sodium bicarbonate was the alkali of choice. Potassium citrate was less efficient. Charts were shown indicating definite impairment of renal function in those patients receiving salicylate alone. The addition of the alkali restored the renal function to normal. Observations on the blood-content and the rate of excretion of the salicylate were also recorded. (This communication has been accepted for publication in the 'Archives of Disease in Childhood.')

6. Dr. John Craig (Aberdeen): 'Malignant Hypertension in a girl of 8.' This case was reported in full in the 'Archives of Disease in Childhood' June 1931, page 157.

7. Dr. R. C. Jewesbury (London): 'Two cases of jaundice in infancy.' His first case was one of grave familial jaundice treated by the injection of whole blood. This was a sixth child and the others had all been affected. The child was born jaundiced, the spleen was enlarged, the liver was not enlarged, the urine contained bilirubin and there was bile present in the stools. The blood count showed 2,560,000 red cells, hæmoglobin 52 per cent. and 26,000 white cells. The child was treated with 8 c.cm. of whole blood injected intramuscularly, and made slow but steady progress. The jaundice cleared at the third month, and the spleen was palpable until the twelfth week. Recovery took place.

The second case, of absence of the hepatic ducts and bile capillaries was an only child, aged 6 months, and had been jaundiced since the second day of life. Bilirubin was present in the

urine, but no urobilinogen, and the stools were pale. The blood serum contained bile pigment and the result of the van den Bergh test was direct. The child died after a month in hospital. The post-mortem showed a liver with signs of slight cirrhosis, but it was otherwise normal The gall-bladder contained bile, which could be squeezed through the cystic and common bile duct into the duodenum. The hepatic ducts were completely absent. Histologically the bile capillaries in the liver were non-existent as such, only being represented by groups of spheroidal cells without definite arrangement. These were surrounded with fibrous tissue and some small round-celled infiltration. When the gall bladder was in contact with the iver the bile capillaries were well formed and canalised.

7. Dr. D. W. Winnicott (London): 'A clinical note on convulsions of infants.' He referred to infantile convulsions without demonstrable physical cause. A boy of 6½ months bit his mother's breast, as infants of that age normally do. When the mother screamed and withdrew he had a convulsion. Henoch (Lectures on Children's Diseases, Sydenham translation, 1889, I, 175) described a girl of 7 months who bit the breast and had a convulsion when the mother screamed. Recent psychological theory laid new emphasis on the intensity of infantile feelings, and suggested that the coincidence was not mere chance. These and similar cases indicated that convulsions were sometimes psychologically determined, and also that maternal over-reaction to normal infantile aggression might underly disturbances of breast feeding.

Second Session (Friday, June 12th, 8.30 p.m.).

8. Dr. G. W. Bray (London) introduced by Dr. D. Paterson: 'Some cases of enuresis of allergic origin.' This communication is reported in full in the present number of the 'Archives of Disease in Childhood.'

9. Dr. A. C. Hampson (London) introduced by Dr. Hector Cameron: 'Tumours of the parathyroid glands.' He described two cases illustrating the effects of hyper-secretion of the parathyroid glands. (1) A boy aged 14 developed genu valgum, associated with generalized hypertrychosis. The deformity progressed, cystic enlargement appeared in a number of bones, and spontaneous fracture occurred in the left femur. All bones showed extreme rarefaction. The blood-calcium was markedly raised and the phosphate diminished; the blood phosphatase was increased; the calcium output in the urine was increased. Improvement followed the removal of a parathyroid cyst. (2) A boy, aged 14, complained of pain in the lower back and legs. Bones showed generalized rarefaction and cyst formation. Metabolic findings were similar to those in Case 1. A malignant tumour was removed from the region of the parathyroid gland. Removal was followed by temporary improvement, but the condition progressed with the appearance of secondary deposits in both kidneys, suprarenals and testes.

10. Dr. K. D. Wilkinson (Birmingham) showed cinematograph films of (1) a case of ectopia cordis; (2) a boy with bilateral Erb's palsy feeding himself with his feet, and other interesting cases.

The Session concluded with a discussion on the Third International Pædiatric Congress to be held in London in 1933, and it was finally decided, if possible, that the meeting should be held in Oxford or Cambridge.

Third Session (Saturday, June 13th, 10 a.m.).

11. Dr. Robert Hutchison (London) with Dr. R. C. Lightwood, introduced by Dr. Thursfield: 'Neoplasm of the Suprarenal Cortex in an Infant aged 4½ months.' They said that this case differed from the classical virilism of the 'infant Hercules' type by combining hypertrichosis with adiposity rather than with excessive muscular development. The symptoms arose at 11 weeks and the authors believed this to be the youngest recorded case of cortical tumour. The clinical course was characterized by increasing adiposity of face, thorax and shoulders; there was anæmia with erythroblastic regeneration. Histologically the tumour consisted of normal cortical cells with a columnar arrangement (diffuse hyperplasia of the cortex). There were no metastases.

12. Dr. J. M. Smellie (Birmingham): 'Sudden death in infancy and childhood.' His remarks were based on a series of 78 autopsies of sudden or unexpected deaths which had been reported to H.M. Coroner, Birmingham. Twenty-four were either stillborn or died within 24 hours of birth. Broncho-pneumonia was the cause of death in 23 cases, most being under twelve months of age and several being suspected cases of suffocation. Seven died from acute gastro-enteritis, six were suffocated, and 5 had congenital heart disease. The causes of death in the

remaining were as follows : acute rheumatic carditis, 2 ; acute nephritis and uræmia, 2 ; œdema of brain, 2 ; miliary tuberculosis, pulmonary embolism, pneumococcal meningitis, diphtheria, choking, suprarenal hæmorrhage, pyo-pneumothorax, and septicæmia, 1 each.

13. Dr. Eric Pritchard (London) : ' The treatment of hydrocephalus.' He showed by means of photographs how cases of hydrocephalus, both internal and external, could be treated by dehydration, i.e., limitation of the intake of fluid, diuresis, diaphoresis, etc. He considered promotion of the ossification of the cranial bones by the administration of vitamin D., irradiation, etc., contributed to the beneficial results of the treatment. The incurable cases of the non-communicating type, arrest of the enlargement of the head could be secured immediately by treatment. Most of the cases of the communicating type could be cured without any deformity, if treatment was commenced early enough.

14. Dr. David Nabarro (London) : ' Congenital syphilis.' He gave some of the results which he had obtained from his experiments with over one thousand cases of inherited syphilis at the Hospital for Sick Children, Great Ormond Street. (1) Whereas only a small percentage of the mothers of syphilitic children had a negative blood Wassermann, nearly 70 per cent. of the 169 fathers examined had a negative Wassermann. (2) The cerebro-spinal fluid was often positive in syphilitic infants, but it frequently became negative after the ordinary treatment by injections. If on re-examination the fluid was found to be still positive, more intensive treatment with special drugs such as tryparsamide, with malaria, etc., was indicated. (3) Typical Hutchinsonian teeth were found in less than 20 per cent. of children over 7, but an equal number showed minor degrees of this defect, and these were sometimes found in mothers, whose latent inherited syphilis could be thus detected. Such mothers might have (a) healthy children ; (b) children with symptoms such as epilepsy, but negative Wassermann reaction ; or (c) syphilitic children with positive Wassermann reaction. The possibility of transmission to the third generation was discussed.

15. Dr. A. P. Thomson (Birmingham) : ' Three cases of cœliac disease.' He described the clinical course of these cases, whose average was fifty-five years. All three had marked steatorrhœa of the cœliac type, a low level of serum calcium, osteoporosis and a flat glucose tolerance curve ; tetany occurred in one case. The clinical history showed that in one instance the condition had existed from childhood, but in two it developed late in life. He thought cases of this type were more frequent than was generally believed and Gee had mentioned them in his original description.

16. Dr. R. W. B. Ellis (London) introduced by Dr. Donald Paterson : ' Some effects of a ketogenic Diet.' He said that the effect of an artificially produced ketosis was observed in patients before and after operation, in two cases of cyclical vomiting, and in two patients who had previously had convulsions with acute infections. In no case were there any symptoms attributable to the ketosis. The effect of a ketogenic diet on the glucose tolerance test was to cause a greatly increased rise in blood sugar, the curve being readjusted toward the normal with insulin. Ten grm. of sodium bicarbonate did not lessen the carbohydrate intolerance, which could not therefore be attributed to acidosis. (This communication has been accepted for publication in the ' Archives of Disease in Childhood.')

17. Dr. Norman Capon (Liverpool) : ' Cystic disease of bone in an infant.' He reported a case of bone disease in an anæmic female infant. X-ray examination showed rarefaction of all the bones, together with clear-cut areas of resorption, especially in the lower end of the femora, in the skull and in the humeri. Wassermann reactions of mother and child were negative and the baby's serum-calcium was 11.24 mgrm. per cent. The patient's condition was rapidly improving without special treatment other than liver extract with iron. It was assumed that the lesions were due to hyper-parathyroidism which was undergoing spontaneous cure.

18. Dr. J. Hartley Gibbens (London) : ' The primary infection of tuberculosis.' He described 3 cases of massive primary tuberculous lesions occurring in young children. The first two cases, brother and sister, had been infected by contact with a phthisical nursemaid and showed interesting and unusual X-ray appearances. The third case was that of an infant of 11 weeks, in contact with its tuberculous mother, who died 3 weeks after its birth, for 36 hours only. The child gained weight steadily, but died at the 11th week. A consistently negative Mantoux test was given throughout.